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 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
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 NEWS 19  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
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 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03  JAPIO has been reloaded and enhanced
 NEWS 24  Sep 16  Experimental properties added to the REGISTRY file
 NEWS 25  Sep 16  Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 26  Sep 16  CA Section Thesaurus available in CAPLUS and CA
 NEWS 27  Oct 01  CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 28  Oct 21  EVENTLINE has been reloaded
 NEWS 29  Oct 24  BEILSTEIN adds new search fields
 NEWS 30  Oct 24  Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 31  Oct 25  MEDLINE SDI run of October 8, 2002
 NEWS 32  Nov 18  DKILIT has been renamed APOLLIT
 NEWS 33  Nov 25  More calculated properties added to REGISTRY
 NEWS 34  Dec 02  TIBKAT will be removed from STN
 NEWS 35  Dec 04  CSA files on STN
 NEWS 36  Dec 17  PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 37  Dec 17  TOXCENTER enhanced with additional content
 NEWS 38  Dec 17  Adis Clinical Trials Insight now available on STN
 NEWS 39  Dec 30  ISMEC no longer available

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L2   ANSWER 1 OF 14922  ADISCTI  COPYRIGHT 2003 (ADIS)
TI   Patients have treatment preferences: a multicentre, double-blind,
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     ADIS TITLE: Rabeprazole vs omeprazole: therapeutic use.
     Peptic ulcer and gastro-oesophageal reflux
     Patient preference.

L2   ANSWER 2 OF 14922  ADISCTI  COPYRIGHT 2003 (ADIS)
TI   Lafutidine-based triple therapy for H. pylori.
     ADIS TITLE: Lafutidine vs lansoprazole: therapeutic use.
     Helicobacter pylori infections
     In combination with amoxicillin + clarithromycin.

L2   ANSWER 3 OF 14922  ADISCTI  COPYRIGHT 2003 (ADIS)
TI   Meta-analysis of esomeprazole 40 mg and lansoprazole 30 mg in
     the healing of reflux oesophagitis.
     ADIS TITLE: Esomeprazole vs lansoprazole: therapeutic use.
     Reflux oesophagitis
     Meta-analysis.

L2   ANSWER 4 OF 14922  ADISCTI  COPYRIGHT 2003 (ADIS)
TI   Esomeprazole and lansoprazole in the management of patients with
     erosive oesophagitis: combining results from two clinical studies.
     ADIS TITLE: Esomeprazole vs lansoprazole: therapeutic use.
     Erosive oesophagitis
     Model of healing and subsequent maintenance therapy.

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TI   Eradication rates of clarithromycin-resistant Helicobacter pylori using
     either rabeprazole or lansoprazole plus amoxicillin and
     clarithromycin.
     ADIS TITLE: Rabeprazole vs lansoprazole: therapeutic use.
     Helicobacter pylori infections
     In combination with amoxicillin and clarithromycin
     Eradication of clarithromycin-resistant H. pylori strains.
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L2 ANSWER 6 OF 14922 ADISCTI COPYRIGHT 2003 (ADIS)
TI Empirical treatment of gastro-oesophageal reflux disease: **lansoprazole** 15 mg once daily equivalent to **lansoprazole** 20 mg once daily.
ADIS TITLE: **Lansoprazole**: therapeutic use.
Gastro-oesophageal reflux
15 vs 30mg once daily.

L2 ANSWER 7 OF 14922 ADISCTI COPYRIGHT 2003 (ADIS)
TI Double blind, randomised, placebo controlled study of four weeks of **lansoprazole** for the treatment of functional dyspepsia in Chinese patients.
ADIS TITLE: **Lansoprazole**: therapeutic use.
Nonulcer dyspepsia
In Chinese patients.

L2 ANSWER 8 OF 14922 ADISCTI COPYRIGHT 2003 (ADIS)
TI Amoxicillin-tetracycline combinations are inadequate as alternative therapies for Helicobacter pylori infection.
ADIS TITLE: Helicobacter pylori eradication therapies: therapeutic use.
Helicobacter pylori infections
Comparison of amoxicillin-based regimens.

L2 ANSWER 9 OF 14922 ADISCTI COPYRIGHT 2003 (ADIS)
TI Randomized double-blind trial with a simplified 6-day-treatment with or without a PPI in children and adolescents with H. pylori gastritis.
ADIS TITLE: Azithromycin + tinidazole +- **lansoprazole**: therapeutic use.
H. pylori infections and gastritis
Six-day regimen.

L2 ANSWER 10 OF 14922 ADISCTI COPYRIGHT 2003 (ADIS)
TI Pharmacokinetic comparison of five proton pump inhibitors.
ADIS TITLE: Proton pump inhibitors: pharmacokinetics.
Single-dose pharmacokinetic comparison
In volunteers.

=> s -lansaprazole
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L3 14 -LANSAPRAZOLE

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L3 ANSWER 1 OF 14 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI External beam radiotherapy (EBRT) in locally advanced pancreatic cancer (LAPC): Ipswich experience.

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TI **Lansaprazole**-associated microscopic colitis: a case series.

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TI Gastro-Oesophageal reflux in the elderly. Role of drug therapy in management.

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TI Study of outcome after targeted intervention for peptic ulcer resistant to acid suppression therapy.

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TI Possibility of chemoprevention by the eradication of Helicobacter pylori: oxidative DNA damage and apoptosis in H. pylori infection.

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TI Hydrogen-potassium ATPase inhibitors induce relaxation on rabbit prostatic strips in vitro.

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TI ME-3407. Antiulcerative.

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TIEN Effect of four lansoprazole dose levels and one dosage regimen of omeprazole on 24-hour intragastric pH in healthy subjects

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TIEN Lansoprazole reduces preoperative gastric fluid acidity and volume in children

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TIEN **Lansaprazole** : a review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficay in acid-related disorders

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TI Efficacy and tolerability of lansoprazole 15mg as maintenance therapy of peptic ulcer

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TI External beam radiotherapy (EBRT) in locally advanced pancreatic cancer (LAPC): Ipswich experience

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TI Pharmacokinetic differences between **lansoprazole** **enantiomers** in rats.

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TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans.

L5 ANSWER 3 OF 229 ADISCTI COPYRIGHT 2003 (ADIS)
TI An enantioselective HPLC method for the determination of optical isomers of **lansoprazole** in human plasma.

L5 ANSWER 4 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Restoration of acid secretion following treatment with proton pump inhibitors.

L5 ANSWER 5 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Application of pharmaceutical principles to clinical practices.

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TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

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TI Stereoselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

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TI Stereoselective metabolism and inhibitory effects of **lansoprazole enantiomers** on human liver CYPS.

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TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes.

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TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: Desired and undesired SH reactions. Impact of chirality.

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TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes.

L5 ANSWER 12 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs.

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TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats.

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TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis.

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TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary phase liquid chromatography and their enantioselective pharmacokinetics in humans.

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TI EFFECTS OF THE **ENANTIOMERS** OF **LANSOPRAZOLE** AG-1749 ON PROTON PLUS POTASSIUM ATPASE ACTIVITY IN CANINE GASTRIC MICROSOMES AND ACID FORMATION IN ISOLATED CANINE PARIETAL CELLS.

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TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19

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TI Stereoselective effects in the separation of **enantiomers** of omeprazole and other substituted benzimidazoles on different chiral stationary phases

L5 ANSWER 19 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Benzimidazole proton pump inhibitor dosage forms

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TI Restoration of acid secretion following treatment with proton pump inhibitors

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TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19

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TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: desired and undesired SH reactions. Impact of chirality

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TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes

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TI Microbial synthesis of a proton pump inhibitor by enantioselective oxidation of a sulfide into its corresponding sulfoxide by Cunninghamella echinulata MK40

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TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes

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TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs

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TI Crystals of benzimidazole compounds

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TI Pharmaceutical preparation for oral application

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TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats

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TI Separation of **lansoprazole enantiomers** in human serum by HPLC

L5 ANSWER 32 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Multiple unit effervescent dosage forms comprising proton pump inhibitor

L5 ANSWER 33 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Optical purification of **enantiomerically** enriched 2-[(arylmethyl)sulfinyl]benzimidazole derivatives

L5 ANSWER 34 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis

L5 ANSWER 35 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Enantioselective preparation of pharmaceutically active sulfoxides by bioreduction

L5 ANSWER 36 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Determination of R(+)- and S(-)-**lansoprazole** using chiral-stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans

L5 ANSWER 37 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Multiple unit pharmaceutical preparations containing proton pump inhibitor

L5 ANSWER 38 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI **Enantiomeric** resolution of chiral sulfoxides on polysaccharide phases by HPLC

L5 ANSWER 39 OF 229 CAPLUS COPYRIGHT 2003 ACS

TI Direct HPLC separation of **enantiomers** of pantoprazole and other benzimidazole sulfoxides using cellulose-based chiral stationary phases in reversed-phase mode

L5 ANSWER 40 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Stereoselective effects in the separation of **enantiomers** of omeprazole and other substituted benzimidazoles on different chiral stationary phases

L5 ANSWER 41 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI **Enantiomerically** pure (pyridylmethylsulfinyl)benzimidazoles useful as drugs, and their preparation from racemates

L5 ANSWER 42 OF 229 CAPLUS COPYRIGHT 2003 ACS
TI Effects of the **enantiomers** of **lansoprazole** (AG-1749) on (hydrogen ion-potassium)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells

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TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

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TI Esomeprazole for acid peptic disorders.

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TI Stereoselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

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TI Stereoselective metabolism and inhibitory effects of **lansoprazole** **enantiomers** on human liver CYPs.

L5 ANSWER 47 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes.

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TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

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TI Stereoselective metabolism and inhibition of **lansoprazole** **enantiomers** on human liver CYPs.

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TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole** **enantiomers** and metabolites in human liver microsomes.

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TI Pharmacokinetic differences between **lansoprazole** **enantiomers** and contribution of cytochrome-P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs.

L5 ANSWER 52 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
TI Pharmacokinetic differences between **lansoprazole** **enantiomers** in rats.

L5 ANSWER 53 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
TI Metabolism of warfarin **enantiomers** in Japanese patients with heart disease having different CYP2C9 and CYP2C19 genotypes.

L5 ANSWER 54 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT

TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis.

L5 ANSWER 55 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans.

L5 ANSWER 56 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
TI Stereoselective Effects in the Separation of **Enantiomers** of Omeprazole and Other Substituted Benzimidazoles on Different Chiral Stationary Phases.

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TI Lack of Effect of **Lansoprazole** on Warfarin Pharmacokinetics and Anticoagulation Effect in Healthy Subjects.

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TI Effects of the **Enantiomers** of **Lansoprazole** (AG-1749) on (H+ + K+)-ATPase Activity in Canine Gastric Microsomes and Acid Formation in Isolated Canine Parietal Cells.

L5 ANSWER 59 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
TI Lack of Effect of **Lansoprazole** on Steady State Warfarin Metabolism.

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TI Restoration of acid secretion following treatment with proton pump inhibitors.

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TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

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TI Proton pump inhibitors - Differences emerge in hepatic metabolism.

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TI New single-isomer compounds on the horizon.

L5 ANSWER 64 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes.

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TI Drug interactions update: Drugs, herbs, and oral anticoagulation.

L5 ANSWER 66 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: Desired and undesired SH reactions. Impact of chirality.

L5 ANSWER 67 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI [Pharmacological testing of proton pump blockers]. PROTONENPUMPENBLOCKER AUF DEM PHARMAKOLOGISCHEN PRUFSTAND.

L5 ANSWER 68 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Clinical pharmacology and safety profile of esomeprazole, the first **enantiomerically** pure proton pump inhibitor.

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TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes.

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TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs.

L5 ANSWER 71 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor, in extensive and poor metabolizers of S-mephenytoin.

L5 ANSWER 72 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI [Old wine in new casks - Are **enantiomers** better drugs?]. ALTER WEIN IN NEUEN SCHLAUCHEN - SIND **ENANTIOMERE** DIE BESSEREN ARZNEIMITTEL?.

L5 ANSWER 73 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats.

L5 ANSWER 74 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Separation of **lansoprazole enantiomers** in human serum by HPLC.

L5 ANSWER 75 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis.

L5 ANSWER 76 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans.

L5 ANSWER 77 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Direct HPLC separation of **enantiomers** of pantoprazole and other benzimidazole sulfoxides using cellulose-based chiral stationary phases in reversed-phase mode.

L5 ANSWER 78 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Stereoselective effects in the separation of **enantiomers** of omeprazole and other substituted benzimidazoles on different chiral stationary phases.

L5 ANSWER 79 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Effects of the **enantiomers** of **lansoprazole** (AG-1749) on (H+ + K+)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells.

L5 ANSWER 80 OF 229 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V.
TI Restoration of acid secretion following treatment with proton pump inhibitors

L5 ANSWER 81 OF 229 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V.
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes

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TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes

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TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats

L5 ANSWER 84 OF 229 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V.

TI Separation of **lansoprazole enantiomers** in human serum by HPLC

L5 ANSWER 85 OF 229 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V.
TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis

L5 ANSWER 86 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID

L5 ANSWER 87 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI PHARMACEUTICAL FORMULATION AND PROCESS

L5 ANSWER 88 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI PACKAGING SYSTEM

L5 ANSWER 89 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORALLY ADMINISTRABLE ACID STABLE ANTIULCER BENZIMIDAZOLE DERIVATIVES; FOR THERAPY AND PROPHYLAXIS OF PEPTIC ULCERS, GASTRO INTESTINAL INFLAMMATORY DISEASES LIKE DUODENAL/GASTRIC ULCER OR GASTRITIS OR OTHER GASTRO INTESTINAL DISORDERS

L5 ANSWER 90 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI NEW PHARMACEUTICAL FORMULATION AND PROCESS; FOR INHIBITING GASTRIC ACID SECRETION IN MAMMALS AND MAN

L5 ANSWER 91 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI SUBSTITUTED BENZIMIDAZOLE DOSAGE FORMS AND METHOD OF USING SAME

L5 ANSWER 92 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID; MULTIPLE UNIT TABLETED DOSAGE FORMS CONTAINING ACID SUSCEPTIBLE PROTON PUMP INHIBITOR IN COMBINATION WITH ONE OR MORE NSAIDS AND WHEREIN AT LEAST PROTON PUMP INHIBITOR IS PROTECTED BY ENTERIC COATED LAYER

L5 ANSWER 93 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORAL ADMINISTRATION FORM FOR AN ACID LIABLE ACTIVE PROTON PUMP INHIBITOR; ANTISECRETORY, GASTROINTESTINAL, ENZYME INHIBITOR NO ENTERIC COATING

L5 ANSWER 94 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE; PROTON PUMP INHIBITOR IS PROTECTED BY AN ENTERIC COATING LAYER AND AN OPTIONAL SEPARATING LAYER IN BETWEEN THE PROTON PUMP INHIBITOR AND THE ENTERIC COATING.

L5 ANSWER 95 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORAL PHARMACEUTICAL DOSAGE FORM; ANTIBACTERIAL COMPOUND, ACID SUSCEPTIBLE PROTON PUMP INHIBITOR(PPI) IN THE FORM OF A MULTIPLE UNIT TABLET; THE PPI IS IN PELLET FORM AND COATED WITH AN ENTERIC POLYMER UNAFFECTED BY COMPRESSION OF PELLETS DURING TABLETING

L5 ANSWER 96 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT; USEFUL IN TREATMENT OF DISORDERS ASSOCIATED WITH GASTRO OESOPHAGEAL REFLUX DISEASES

L5 ANSWER 97 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI METHOD OF MAKING A PHARMACEUTICAL DOSAGE FORM COMPRISING A PROTON PUMP INHIBITOR; FORMING A CORE MATERIAL COMPRISING A PROTON PUMP INHIBITOR AND AN ALKALINE REACTING COMPOUND, APPLYING AN ENTERIC POLYMER LAYER TO SURROUND THE CORE THEREBY FORMING IN SITU A SEPARATING LAYER AS A SALT OF POLYMER AND ALKALINE COMPOUND

L5 ANSWER 98 OF 229 IFIPAT COPYRIGHT 2003 IFI
TI VETERINARY COMPOSITION; ANTISECRETORY

L5 ANSWER 99 OF 229 IPA COPYRIGHT 2003 ASHP

TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19

L5 ANSWER 100 OF 229 IPA COPYRIGHT 2003 ASHP

TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans

L5 ANSWER 101 OF 229 JICST-EPlus COPYRIGHT 2003 JST
TI Pharmacokinetic Differences between **Lansoprazole Enantiomers** and Contribution of Cytochrome P450 Isoforms to Enantioselective Metabolism of **Lansoprazole** in Dogs.

L5 ANSWER 102 OF 229 MEDLINE
TI Restoration of acid secretion following treatment with proton pump inhibitors.

L5 ANSWER 103 OF 229 MEDLINE
TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.

L5 ANSWER 104 OF 229 MEDLINE
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes.

L5 ANSWER 105 OF 229 MEDLINE
TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: desired and undesired SH reactions. Impact of chirality.

L5 ANSWER 106 OF 229 MEDLINE
TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes.

L5 ANSWER 107 OF 229 MEDLINE
TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs.

L5 ANSWER 108 OF 229 MEDLINE
TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats.

L5 ANSWER 109 OF 229 MEDLINE
TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis.

L5 ANSWER 110 OF 229 MEDLINE
TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans.

L5 ANSWER 111 OF 229 MEDLINE
TI Effects of the **enantiomers** of **lansoprazole** (AG-1749) on (H+ + K+)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells.

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RESERVED.
TIEN Restoration of acid secretion following treatment with proton pump inhibitors

L5 ANSWER 113 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19

L5 ANSWER 114 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes

L5 ANSWER 115 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes

L5 ANSWER 116 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs

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TIEN Pharmacokinetic differences between **lansoprazole enantiomers** in rats

L5 ANSWER 118 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN Separation of **lansoprazole enantiomers** in human serum by HPLC

L5 ANSWER 119 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis

L5 ANSWER 120 OF 229 PASCAL COPYRIGHT 2003 INIST-CNRS. ALL RIGHTS RESERVED.
TIEN Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans

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TIEN Effects of the **enantiomers** of **lansoprazole** (AG-1749) on (H.sup.+ + K.sup.+)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells

L5 ANSWER 122 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Restoration of acid secretion following treatment with proton pump inhibitors

L5 ANSWER 123 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Proton pump inhibitors - differences emerge in hepatic metabolism

L5 ANSWER 124 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19

L5 ANSWER 125 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Stereoselective metabolism and inhibitory effects of **lansoprazole enantiomers** on human liver CYPs.

L5 ANSWER 126 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes

L5 ANSWER 127 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: Desired and undesired SH reactions. Impact of chirality

L5 ANSWER 128 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Clinical pharmacology and safety profile of esomeprazole, the first **enantiomerically** pure proton pump inhibitor

L5 ANSWER 129 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI High-performance liquid chromatographic assay for the simultaneous determination of **lansoprazole enantiomers** and metabolites in human liver microsomes

L5 ANSWER 130 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs

L5 ANSWER 131 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Spectrophotometric methods for the determination of **lansoprazole** and pantoprazole sodium sesquihydrate

L5 ANSWER 132 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Stereoselective metabolism by human liver CYP enzymes of a substituted benzimidazole

L5 ANSWER 133 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats

L5 ANSWER 134 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Separation of **lansoprazole enantiomers** in human serum by HPLC

L5 ANSWER 135 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis

L5 ANSWER 136 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI DETERMINATION OF R(+)-**LANSOPRAZOLE** AND S(-)-**LANSOPRAZOLE** USING CHIRAL STATIONARY-PHASE LIQUID-CHROMATOGRAPHY AND THEIR ENANTIOSELECTIVE PHARMACOKINETICS IN HUMANS

L5 ANSWER 137 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI DIRECT HPLC SEPARATION OF **ENANTIOMERS** OF PANTOPRAZOLE AND OTHER BENZIMIDAZOLE SULFOXIDES USING CELLULOSE-BASED CHIRAL STATIONARY PHASES IN REVERSED-PHASE MODE

L5 ANSWER 138 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI PHARMACOKINETIC PROPERTIES OF A NOVEL GASTRIC PROTON PUMP INHIBITOR, (+/-)-2-[(4-METHOXY-6,7,8,9-TETRAHYDRO-5H-CYCLOHEPTA[B]PYRIDIN-9-YL)SULFINYL]-1H-BENZIMIDAZOLE SODIUM-SALT, IN HEALTHY-SUBJECTS

L5 ANSWER 139 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
TI EFFECTS OF THE **ENANTIOMERS** OF **LANSOPRAZOLE** (AG-1749) ON (H+ (K+)-ATPASE ACTIVITY IN CANINE GASTRIC MICROSOMES AND ACID

FORMATION IN ISOLATED CANINE PARIETAL-CELLS)

L5 ANSWER 140 OF 229 TOXCENTER COPYRIGHT 2003 ACS
TI Application of pharmaceutical principles to clinical practices

L5 ANSWER 141 OF 229 TOXCENTER COPYRIGHT 2003 ACS
TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: Desired and undesired SH reactions. Impact of chirality

L5 ANSWER 142 OF 229 TOXCENTER COPYRIGHT 2003 ACS
TI Microbial synthesis of a proton pump inhibitor by enantioselective oxidation of a sulfide into its corresponding sulfoxide by Cunninghamella echinulata MK40

L5 ANSWER 143 OF 229 TOXCENTER COPYRIGHT 2003 ACS
TI Crystals of benzimidazole compounds

L5 ANSWER 144 OF 229 TOXCENTER COPYRIGHT 2003 ACS
TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs

L5 ANSWER 145 OF 229 USPATFULL
TI Nucleic acids for the prevention and treatment of gastric ulcers

L5 ANSWER 146 OF 229 USPATFULL
TI Cyclooxygenase-2 inhibitors, compositions and methods of use

L5 ANSWER 147 OF 229 USPATFULL
TI Substituted benzimidazole dosage forms and method of using same

L5 ANSWER 148 OF 229 USPATFULL
TI Oral pharmaceutical dosage forms comprising a proton pump inhibitor and a NSAID

L5 ANSWER 149 OF 229 USPATFULL
TI Method for the administration of acid-labile drugs

L5 ANSWER 150 OF 229 USPATFULL
TI Benzimidazole compound crystal

L5 ANSWER 151 OF 229 USPATFULL
TI Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use related applications

L5 ANSWER 152 OF 229 USPATFULL
TI S-rabeprazole compositions and methods

L5 ANSWER 153 OF 229 USPATFULL
TI USE OF 7-(2-OXA-5,8-DIAZABICYLCO[4.3.0]NON-8-YL)-QUINOLONE CARBOXYLIC ACID AND NAPHTHYRIDON CARBOXYLIC ACID DERIVATIVES FOR THE TREATMENT OF HELIOBACTER PYLORI INFECTIONS AND ASSOCIATED GASTRODUODENAL DISEASES

L5 ANSWER 154 OF 229 USPATFULL
TI Hydroxylansoprazole methods

L5 ANSWER 155 OF 229 USPATFULL
TI Novel suppository form comprising an acid-labile active compound

L5 ANSWER 156 OF 229 USPATFULL
TI Methods and compositions using (-) norcisapride in combination with proton pump inhibitors or H2 receptor antagonists

L5 ANSWER 157 OF 229 USPATFULL

TI Methods and compositions using (+) norcisapride in combination with proton pump inhibitors or H2 receptor antagonists

L5 ANSWER 158 OF 229 USPATFULL
TI Pharmaceutical formulation and process

L5 ANSWER 159 OF 229 USPATFULL
TI Chemical process and pharmaceutical formulation

L5 ANSWER 160 OF 229 USPATFULL
TI Suppository form comprising an acid-labile active compound

L5 ANSWER 161 OF 229 USPATFULL
TI Stable multi-unitary pharmaceutical preparations containing substituted benzimidazoles

L5 ANSWER 162 OF 229 USPATFULL
TI High-throughput formation, identification, and analysis of diverse solid-forms

L5 ANSWER 163 OF 229 USPATFULL
TI Milled particles

L5 ANSWER 164 OF 229 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same

L5 ANSWER 165 OF 229 USPATFULL
TI Packaging system

L5 ANSWER 166 OF 229 USPATFULL
TI R-**lansoprazole** compositions and methods

L5 ANSWER 167 OF 229 USPATFULL
TI Oral pharmaceutical dosage forms comprising a proton pump inhibitor and a NSAID

L5 ANSWER 168 OF 229 USPATFULL
TI Orally administrable acid stable antiulcer benzimidazole derivatives

L5 ANSWER 169 OF 229 USPATFULL
TI Methods and compositions using (-) norcisapride in combination with proton pump inhibitors or H2 receptor antagonists

L5 ANSWER 170 OF 229 USPATFULL
TI Dual enhancer composition for topical and transdermal drug delivery

L5 ANSWER 171 OF 229 USPATFULL
TI Method and compositions using (+) norcisapride in combination with proton pump inhibitors or H2 receptor antagonist

L5 ANSWER 172 OF 229 USPATFULL
TI Novel administration form comprising an acid-labile active compound

L5 ANSWER 173 OF 229 USPATFULL
TI NEW PHARMACEUTICAL FORMULATION AND PROCESS

L5 ANSWER 174 OF 229 USPATFULL
TI CONTROLLED-RELEASE NANOPARTICULATE COMPOSITIONS

L5 ANSWER 175 OF 229 USPATFULL
TI Hydroxyomeprazole compositions

L5 ANSWER 176 OF 229 USPATFULL
TI Media milling

L5 ANSWER 177 OF 229 USPATFULL
TI Hydroxylansoprazole compositions and methods

L5 ANSWER 178 OF 229 USPATFULL
TI Hydroxide-releasing agents as skin permeation enhancers

L5 ANSWER 179 OF 229 USPATFULL
TI Oral administration form for an acid liable active proton pump inhibitor

L5 ANSWER 180 OF 229 USPATFULL
TI Methods for controlling gram negative bacteria in mammals

L5 ANSWER 181 OF 229 USPATFULL
TI Nitrosated and nitrosylated cyclooxygenase-2 inhibitors, compositions and methods of use

L5 ANSWER 182 OF 229 USPATFULL
TI Imidazo pyridine derivatives which inhibit gastric acid secretion

L5 ANSWER 183 OF 229 USPATFULL
TI Imidazo pyridine derivatives which inhibit gastric acid secretion

L5 ANSWER 184 OF 229 USPATFULL
TI Use of 7-(1-aminomethyl-2-oxa-7-aza-bicyclo[3.3.0]oct-7-yl)-quinolonecarboxylic acid and -naphthyridonecarboxylic acid derivatives for the therapy of Helicobacter pylori infections and associated gastroduodenal disorders

L5 ANSWER 185 OF 229 USPATFULL
TI S-rabeprazole compositions and methods

L5 ANSWER 186 OF 229 USPATFULL
TI Process for preparing omeprzole

L5 ANSWER 187 OF 229 USPATFULL
TI Use of an H+, K+-ATPase inhibitor in the treatment of widal's syndrome

L5 ANSWER 188 OF 229 USPATFULL
TI S-**lansoprazole** compositions and methods

L5 ANSWER 189 OF 229 USPATFULL
TI Hydroxyomeprazole compositions and methods

L5 ANSWER 190 OF 229 USPATFULL
TI Use of 7-(1-aminomethyl-2-oxa-7-aza-bicyclo[3.3.0]oct-7-yl)-quinolone carboxylic acid and naphthyridone carboxylic acid derivatives for treating Helicobacter pylori infections and the gastroduodenal diseases associated therewith

L5 ANSWER 191 OF 229 USPATFULL
TI Use of an H+, K+-atpase inhibitor in the treatment of nasal polyps

L5 ANSWER 192 OF 229 USPATFULL
TI Multiple unit effervescent dosage form

L5 ANSWER 193 OF 229 USPATFULL
TI Methods for controlling gram negative bacteria in mammals with bicyclo spiroether compounds

L5 ANSWER 194 OF 229 USPATFULL
TI ADMINISTRATION OF PHARMACEUTICALS

L5 ANSWER 195 OF 229 USPATFULL

TI Oral pharmaceutical dosage forms comprising a proton pump inhibitor and an antacid agent or alginate

L5 ANSWER 196 OF 229 USPATFULL
TI R-rabeprazole compositions and methods

L5 ANSWER 197 OF 229 USPATFULL
TI Pyridylthio compounds for controlling helicobacter bacteria

L5 ANSWER 198 OF 229 USPATFULL
TI Oral pharmaceutical dosage form

L5 ANSWER 199 OF 229 USPATFULL
TI Use of 7-(2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-quinolone carboxylic acid and naphthyridon carboxylic acid derivatives for the treatment of Helicobacter pylori infections and associated gastroduodenal diseases

L5 ANSWER 200 OF 229 USPATFULL
TI Oral pharmaceutical dosage forms comprising a proton pump inhibitor and a prokinetic agent

L5 ANSWER 201 OF 229 USPATFULL
TI Multiple unit effervescent dosage forms comprising proton pump inhibitor

L5 ANSWER 202 OF 229 USPATFULL
TI Process for the preparation of a magnesium salt of a substituted sulfinyl heterocycle

L5 ANSWER 203 OF 229 USPATFULL
TI Thiopyridines for use in the control of helicobacter bacteria

L5 ANSWER 204 OF 229 USPATFULL
TI Thiadiazole compounds useful as inhibitors of H.sup.+ /K.sup.+ atpase

L5 ANSWER 205 OF 229 USPATFULL
TI Benzimidazole derivatives as antiulcer agents, process for their preparation and pharmaceutical compositions containing them

L5 ANSWER 206 OF 229 USPATFULL
TI Immediate release pH-independent solid dosage form of cisapride

L5 ANSWER 207 OF 229 USPATFULL
TI Methods for controlling gram negative bacteria in mammals

L5 ANSWER 208 OF 229 USPATFULL
TI Method of making a pharmaceutical dosage form comprising a proton pump inhibitor

L5 ANSWER 209 OF 229 USPATFULL
TI Process for synthesis of substituted sulphoxides

L5 ANSWER 210 OF 229 USPATFULL
TI Process for the optical purification of **enantiomerically** enriched benzimidazole derivatives

L5 ANSWER 211 OF 229 USPATFULL
TI Piperazinothiopyridines for the control of Helicobacter bacteria

L5 ANSWER 212 OF 229 USPATFULL
TI Substituted arylalkylthioalkylthiopyridines for use in the control of helicobacter bacteria

L5 ANSWER 213 OF 229 USPATFULL
TI Preparation of pharmaceutically active compounds by biooxidation

L5 ANSWER 214 OF 229 USPATFULL
TI Multiple unit tableted dosage form of omeprazole

L5 ANSWER 215 OF 229 USPATFULL
TI Urea and thiourea derivatives of azolones

L5 ANSWER 216 OF 229 USPATFULL
TI Multiple unit pharmaceutical preparation

L5 ANSWER 217 OF 229 USPATFULL
TI Histidine compositions and methods for treating or preventing infectious and non-infectious diarrheas

L5 ANSWER 218 OF 229 USPATFULL
TI Veterinary composition

L5 ANSWER 219 OF 229 USPATFULL
TI Sulfonamide compounds of azolones anti-helicobacter agents

L5 ANSWER 220 OF 229 USPATFULL
TI Method for treatment of psoriasis, by omeprazole or related compounds

L5 ANSWER 221 OF 229 USPATFULL
TI Ester and carbamate derivatives of azolones

L5 ANSWER 222 OF 229 USPATFULL
TI Substituted azolone derivatives

L5 ANSWER 223 OF 229 USPATFULL
TI Urea and thiourea derivatives of azolones

L5 ANSWER 224 OF 229 USPATFULL
TI Acyl derivatives of azolones

L5 ANSWER 225 OF 229 USPATFULL
TI Heterocyclic derivatives of azolones

L5 ANSWER 226 OF 229 USPATFULL
TI 4-quinolinyl derivatives

L5 ANSWER 227 OF 229 USPATFULL
TI Sulfonamide derivatives of azolones

L5 ANSWER 228 OF 229 USPAT2
TI Hydroxyomeprazole compositions

L5 ANSWER 229 OF 229 USPAT2
TI Use of an H+, K+-atpase inhibitor in the treatment of nasal polyps

=> d 108 101 83 76 72 68 52 all

L5 ANSWER 108 OF 229 MEDLINE
AN 1999093136 MEDLINE
DN 99093136 PubMed ID: 9877309
TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats.
AU Arimori K; Yasuda K; Katsuki H; Nakano M
CS Department of Pharmacy, Kumamoto University Hospital, Japan.
SO JOURNAL OF PHARMACY AND PHARMACOLOGY, (1998 Nov) 50 (11) 1241-5.
Journal code: 0376363. ISSN: 0022-3573.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

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FS Priority Journals
EM 199904
ED Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990426
AB Because limited information is available about potential differences between the pharmacokinetics and pharmacodynamics of the **enantiomers** of **lansoprazole**, the enantioselective pharmacokinetics of the compound have been investigated in rats. There was a noticeable difference between the serum levels of the **enantiomers** of **lansoprazole** and of their metabolites, 5-hydroxylansoprazole **enantiomers**, after oral administration of the racemate (50 mg kg(-1)) to rats. Cmax (maximum serum concentration) and AUC (area under the serum concentration-time curve) for (+)-**lansoprazole** were 5-6 times greater than those for (-)-**lansoprazole**, whereas for (+)-5-hydroxylansoprazole both values were significantly smaller than those for the (-) **enantiomer**. CLtot/F values (where CLtot is total clearance and F is the fraction of the dose absorbed) for (+)-**lansoprazole** were significantly smaller than those for the (-) **enantiomer**. There was no significant difference between the absorption rate constants of the **lansoprazole enantiomers** in the in-situ absorption study. The in-vitro protein-binding study showed that binding of (+)-**lansoprazole** to rat serum proteins was significantly greater than for the (-) **enantiomer**. The in-vitro metabolic study showed that the mean metabolic ratio (45.9%) for (-)-**lansoprazole** was significantly greater than that (19.8%) for the (+) **enantiomer** in rat liver microsomes at 5.6 microM **lansoprazole**. These results show that the enantioselective disposition of **lansoprazole** could be a consequence of the enantioselectivity of plasma-protein binding and the hepatic metabolism of the **enantiomers**.
CT Check Tags: Animal; In Vitro; Male
Anesthesia
*Anti-Ulcer Agents: ME, metabolism
Area Under Curve
Chromatography, High Pressure Liquid
Fasting
Molecular Structure
*Omeprazole: AA, analogs & derivatives
Omeprazole: IP, isolation & purification
Omeprazole: ME, metabolism
Protein Binding
Rats
Rats, Wistar
Stereoisomerism
RN **103577-45-3 (lansoprazole)**; 73590-58-6 (Omeprazole)
CN 0 (Anti-Ulcer Agents)

L5 ANSWER 101 OF 229 JICST-EPlus COPYRIGHT 2003 JST
AN 1010305021 JICST-EPlus
TI Pharmacokinetic Differences between **Lansoprazole** **Enantiomers** and Contribution of Cytochrome P450 Isoforms to Enantioselective Metabolism of **Lansoprazole** in Dogs.
AU MASA K; HAMADA A; ARIMORI K; FUJII J; NAKANO M
CS Kumamoto Univ. Hospital, Kumamoto, Jpn
SO Biol Pharm Bull, (2001) vol. 24, no. 3, pp. 274-277. Journal Code: S0989A (Fig. 5, Tbl. 1, Ref. 16)
ISSN: 0918-6158
CY Japan
DT Journal; Article
LA English
STA New
AB The purpose of this study was to evaluate the pharmacokinetics of

lansoprazole enantiomers and contribution of cytochrome P450 enzymes to enantioselective metabolism in dogs. The mean CMAX and area under the curve (AUC) values of (+)-**lansoprazole** were 4-5 times greater than those of (-)-**lansoprazole** following oral administration of 30-mg racemic **lansoprazole** to dogs. The CLtot/F values of (+)-**lansoprazole** were significantly smaller than those of (-)-**lansoprazole** ($p<0.05$). The mean unbound fraction of (-)-**lansoprazole** was significantly greater than that of the (+)-**lansoprazole**. The amount of (+)-**lansoprazole** remaining was significantly greater than that of the (-)-**lansoprazole** after incubation of racemic **lansoprazole** in dog liver microsomes. When the effects of ticlopidine or ketoconazole on the metabolism of **lansoprazole** were studied using dog liver microsomes, ticlopidine significantly inhibited the formation of 5-hydroxylansoprazole, but not another metabolite, **lansoprazole** sulfone; however ketoconazole significantly inhibited formation of both metabolites. When the amount of (+)- and (-)-**enantiomers** remaining was measured in the presence and absence of ticlopidine, the amount of (+)-**lansoprazole** was significantly greater than that of the (-)-**lansoprazole**. On the other hand, there was no significant difference between the amount of (+)- and (-)-**enantiomers** remaining in combination with ketoconazole. These results suggest that the enantioselective pharmacokinetics of **lansoprazole enantiomers** are probably ascribable to their enantioselective protein binding and/or metabolism, and among the cytochrome P450 enzymes, CYP3A contributed to the enantioselective metabolism of **lansoprazole**. (author abst.)

CC GY01021U; GV01070X (615.45.033; 615.2.015.2)

CT gastric secretory inhibitor; racemic modification; **enantiomer**; pharmacokinetics; stereospecificity; drug metabolism; cytochrome P450; isozyme; oral administration; dog; plasma concentration; AUC(pharmacokinetics); protein binding; drug interaction; anticoagulant; antifungal drug; ether; sulfoxide; nitrogen heterocyclic compound; polynuclear aromatic compound; organofluorine compound; aromatic chlorine compound; sulfur heterocyclic compound; carboxamide; phenol ether; oxygen heterocyclic compound; fatty acid

BT gastrointestinal drug; drug; stereoisomer; isomer(molecule); dynamics; steric effect; effect; metabolism; cytochrome; hemoprotein; iron protein; metalloprotein; chromoprotein; protein; hydroxylase; oxidoreductase; enzyme; administration route; administration(biology); Canidae; Carnivora; Mammalia; Vertebrata; animal; blood concentration; concentration(ratio); degree; binding and coupling; interaction; hematological drug; antimicrobial drug; organosulphur compound; heterocyclic compound; aromatic compound; organohalogene compound; aromatic halogen compound; organochlorine compound; aliphatic carboxylic acid; carboxylic acid

L5 ANSWER 83 OF 229 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V.

AN 1998276357 ESBIOBASE

TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats

AU Arimori K.; Yasuda K.; Katsuki H.; Nakano M.

CS M. Nakano, Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860-8556, Japan.

SO Journal of Pharmacy and Pharmacology, (1998), 50/11 (1241-1245), 16 reference(s)
CODEN: JPPMAB ISSN: 0022-3573

DT Journal; Article

CY United Kingdom

LA English

SL English

AB Because limited information is available about potential differences between the pharmacokinetics and pharmacodynamics of the **enantiomers** of **lansoprazole**, the enantioselective pharmacokinetics of the compound have been investigated in rats. There

was a noticeable difference between the serum levels of the **enantiomers** of **lansoprazole** and of their metabolites, 5-hydroxylansoprazole **enantiomers**, after oral administration of the racemate (50 mg kg.sup.-.sup.1) to rats. C(max) (maximum serum concentration) and AUC (area under the serum concentration-time curve) for (+)-**lansoprazole** were 5-6 times greater than those for (-)-**lansoprazole**, whereas for (+)-5-hydroxylansoprazole both values were significantly smaller than those for the (-) **enantiomer**. CL(tot)/F values (where CL(tot) is total clearance and F is the fraction of the dose absorbed) for (+)-**lansoprazole** were significantly smaller than those for the (-) **enantiomer**. There was no significant difference between the absorption rate constants of the **lansoprazole enantiomers** in the insitu absorption study. The in-vitro protein-binding study showed that binding of (+) **lansoprazole** to rat serum proteins was significantly greater than for the (-) **enantiomer**. The in-vitro metabolic study showed that the mean metabolic ratio (45.9%) for (-)**lansoprazole** was significantly greater than that (19.8%) for the (+) **enantiomer** in rat liver microsomes at 5.6 .mu.M **lansoprazole**. These results show that the enantioselective disposition of **lansoprazole** could be a consequence of the enantioselectivity of plasma-protein binding and the hepatic metabolism of the **enantiomers**.

CC 99 General

L5 ANSWER 76 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 96125822 EMBASE
DN 1996125822
TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans.
AU Katsuki H.; Yagi H.; Arimori K.; Nakamura C.; Nakano M.; Katafuchi S.; Fujioka Y.; Fujiyama S.
CS Department of Pharmacy, Kumamoto University Hospital,Kumamoto, Japan
SO Pharmaceutical Research, (1996) 13/4 (611-615).
ISSN: 0724-8741 CODEN: PHREEB
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Purpose. Stereoselective and sensitive methods employing chiral stationary phase columns for HPLC determination of **enantiomers** of **lansoprazole** in the human serum were developed and pharmacokinetic behaviors of the **enantiomers** were evaluated in seven subjects. Methods. Five chiral stationary phase columns: Chiralcel OD (cellulose tris(3,5-dimethyi-phenylcarbamate)), OF (cellulose tris(4-chlorophenylcarbamate)), OF (cellulose tris(4-methylphenylcarbamate)) and OJ (cellulose tris(4-methylbenzoate)), and Chiralpak AS (amylose tris ((S)-1-phenylethylcarbamate)) were investigated. Results, Chiralcel OD and Chiralpak AS columns gave a good resolution of R(+)- and S(-)-**enantiomers** from racemic **lansoprazole**, but Chiralcel OF, OF, and OJ did not. The mean C(max) and the AUC values of R(+)-**enantiomer** were 3-5 times greater than those of S(-) **enantiomer** following oral administration of 30 mg of racemic **lansoprazole**. The C(max) values of R(+)-**enantiomer** were significantly smaller than those of S(-)-**enantiomer**. Binding of R(+)-**enantiomer** to human serum proteins was significantly greater than that of S(-)-**enantiomer**. The mean metabolic ratio (metabolites/parent compound) in human liver microsomes of S(-)-**enantiomer** was significantly greater than that of R(+)-**enantiomer**. Conclusions. The stereoselective pharmacokinetics of **lansoprazole enantiomers** is likely due to its

stereoselective protein binding and/or metabolism.
CT Medical Descriptors:
*pharmacokinetics
*stereospecificity
adult
article
chirality
clinical trial
drug blood level
drug metabolism
drug protein binding
enantiomer
female
high performance liquid chromatography
human
human experiment
male
normal human
oral drug administration
priority journal
volunteer
Drug Descriptors:
***lansoprazole: CT, clinical trial**
***lansoprazole: CR, drug concentration**
***lansoprazole: PK, pharmacokinetics**
RN (**lansoprazole**) 103577-45-3

L5 ANSWER 72 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000425740 EMBASE
TI [Old wine in new casks - Are **enantiomers** better drugs?].
ALTER WEIN IN NEUEN SCHLAUCHEN - SIND **ENANTIOMERE** DIE BESSEREN ARZNEIMITTEL?.
AU Klotz U.; Roots I.
CS Dr. U. Klotz, Dr. Margarete Fischer-Bosch-Institut, Klinische Pharmakologie, Auerbachstrasse 112, D-70376 Stuttgart, Germany
SO Verdauungskrankheiten, (2000) 18/5 (240-242).
Refs: 10
ISSN: 0174-738X CODEN: VERDEJ
CY Germany
DT Journal; (Short Survey)
FS 030 Pharmacology
037 Drug Literature Index
LA German
CT Medical Descriptors:
*drug metabolism
enantiomer
multidrug resistance
stereochemistry
drug clearance
gastrointestinal symptom
human
short survey
Drug Descriptors:
*proton pump inhibitor: PK, pharmacokinetics
omeprazole: PK, pharmacokinetics
esomeprazole: PK, pharmacokinetics
omeprazole derivative: PK, pharmacokinetics
lansoprazole
pantoprazole
rabeprazole
glycoprotein P
beta adrenergic receptor blocking agent
analgesic agent
anticonvulsive agent

anticoagulant agent
antihistaminic agent
local anesthetic agent
antiarrhythmic agent
quinidine
antimalarial agent
quinine
ketamine
unclassified drug

RN (omeprazole) 73590-58-6, 95510-70-6; (**lansoprazole**) 103577-45-3; (pantoprazole) 102625-70-7; (rabeprazole) 117976-89-3, 117976-90-6; (quinidine) 56-54-2; (quinine) 130-89-2, 130-95-0, 14358-44-2, 549-48-4, 549-49-5, 60-93-5, 7549-43-1; (ketamine) 1867-66-9, 6740-88-1, 81771-21-3

L5 ANSWER 68 OF 229 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2001377148 EMBASE

TI Clinical pharmacology and safety profile of esomeprazole, the first **enantiomerically** pure proton pump inhibitor.

AU Tonini M.; Vigneri S.; Savarino V.; Scarpignato C.

CS Prof. M. Tonini, Dipt. di Scienze Fisiol.-Farmacol., Universita di Pavia, Piazza Botta 10, 27100 Pavia, Italy. marcello.tonini@unipv.it

SO Digestive and Liver Disease, (2001) 33/7 (600-606).
Refs: 41
ISSN: 1125-8055 CODEN: DLDIFK

CY Italy

DT Journal; Article

FS 004 Microbiology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology

LA English

SL English

AB Awareness of important differences in the pharmacological profile of individual optical isomers of chiral drugs led to the development of esomeprazole, the S-isomer of omeprazole, a new pharmacological entity designed to improve the clinical outcome of available proton pump inhibitors in the management of acid-related disorders. The superior acid control achieved by esomeprazole is mainly due to an advantageous metabolism compared with racemate omeprazole, leading to improved bioavailability and to enhanced delivery of the drug to the gastric proton pump.

CT Medical Descriptors:
clinical pharmacology
drug safety
enantiomer
drug purity
isomerism
chirality
treatment outcome
hyperactivity: DT, drug therapy
disease management
stomach acid
disease control
drug metabolism
drug bioavailability
drug delivery system
drug half life
sex difference
headache: SI, side effect
abdominal pain: SI, side effect
diarrhea: SI, side effect
Helicobacter pylori

human
male
female
clinical trial
randomized controlled trial
double blind procedure
crossover procedure
controlled study
article
Drug Descriptors:
*esomeprazole: AE, adverse drug reaction
*esomeprazole: CT, clinical trial
*esomeprazole: CB, drug combination
*esomeprazole: CM, drug comparison
*esomeprazole: CR, drug concentration
*esomeprazole: DV, drug development
*esomeprazole: IT, drug interaction
*esomeprazole: DT, drug therapy
*esomeprazole: PK, pharmacokinetics
*esomeprazole: PD, pharmacology
*esomeprazole: PO, oral drug administration
proton pump inhibitor: AE, adverse drug reaction
proton pump inhibitor: CT, clinical trial
proton pump inhibitor: CB, drug combination
proton pump inhibitor: CM, drug comparison
proton pump inhibitor: CR, drug concentration
proton pump inhibitor: DV, drug development
proton pump inhibitor: IT, drug interaction
proton pump inhibitor: DT, drug therapy
proton pump inhibitor: PK, pharmacokinetics
proton pump inhibitor: PD, pharmacology
proton pump inhibitor: PO, oral drug administration
omeprazole: CT, clinical trial
omeprazole: CM, drug comparison
omeprazole: DT, drug therapy
omeprazole: PK, pharmacokinetics
omeprazole: PD, pharmacology
omeprazole: PO, oral drug administration
pantoprazole: CT, clinical trial
pantoprazole: CM, drug comparison
pantoprazole: DT, drug therapy
pantoprazole: PO, oral drug administration
lansoprazole: CT, clinical trial
lansoprazole: CM, drug comparison
lansoprazole: DT, drug therapy
lansoprazole: PO, oral drug administration
rabeprazole: CT, clinical trial
rabeprazole: CM, drug comparison
rabeprazole: DT, drug therapy
rabeprazole: PO, oral drug administration
diazepam: CB, drug combination
diazepam: IT, drug interaction
diazepam: PK, pharmacokinetics
phenytoin: CB, drug combination
phenytoin: IT, drug interaction
phenytoin: PK, pharmacokinetics
warfarin: CB, drug combination
warfarin: IT, drug interaction
warfarin: PK, pharmacokinetics
clarithromycin: CB, drug combination
clarithromycin: IT, drug interaction
clarithromycin: PK, pharmacokinetics
quinidine: CB, drug combination
quinidine: IT, drug interaction

quinidine: PK, pharmacokinetics
cisapride: CB, drug combination
cisapride: IT, drug interaction
cisapride: PK, pharmacokinetics

RN (esomeprazole) 119141-88-7, 202742-32-3, 217087-09-7, 217087-10-0; (omeprazole) 73590-58-6, 95510-70-6; (pantoprazole) 102625-70-7; (**lansoprazole**) 103577-45-3; (rabeprazole) 117976-89-3, 117976-90-6; (diazepam) 439-14-5; (phenytoin) 57-41-0, 630-93-3; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (clarithromycin) 81103-11-9; (quinidine) 56-54-2; (cisapride) 81098-60-4

L5 ANSWER 52 OF 229 DRUGU COPYRIGHT 2003 THOMSON DERWENT
AN 1999-05419 DRUGU P
TI Pharmacokinetic differences between **lansoprazole** **enantiomers** in rats.
AU Arimori K; Yasuda K; Katsuki H; Nakano M
CS Univ.Kumamoto
LO Kumamoto, Jap.
SO J.Pharm.Pharmacol. (50, No. 11, 1241-45, 1998) 2 Fig. 2 Tab. 16 Ref.
CODEN: JPPMAB ISSN: 0022-3573
AV Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860-8556, Japan.
LA English
DT Journal
AB In rats after p.o. **lansoprazole** (LS, Takeda), there were significant differences between serum levels of (+)-LS and (-)-LS) and metabolites, (+)-and (-)-5-hydroxylansoprazole (OHLS). Cmax and AUC values for (+)-LS were greater than those for (-)-LS, whereas for (+)-OHLS both values were smaller than those for (-)-OHLS. There was no significant difference between the absorption rate constants of the LS **enantiomers** in an in-situ absorption study. The in-vitro binding of (+)-LS to rat serum proteins was significantly greater than for (-)-LS. The results indicated that the enantioselective disposition of LS may be due to enantioselectivity of plasma-protein binding and the hepatic metabolism of the **enantiomers**.
SH P Pharmacology
CC 8 Pharmacokinetics
16 Gastrointestinal
CT [01] **LANSOPRAZOLE** *DM; TAKEDA *FT; AG-1749 *RN; RAT *FT; IN-VIVO *FT; IN-VITRO *FT; LIVER *FT; MICROSOME-DRUG-METAB. *FT; STEREOSELECTIVE *FT; LEVO-ISOMER *FT; DEXTRO-ISOMER *FT; METABOLITE *FT; BIOSYNTH. *FT; HALF-LIFE *FT; CONC. *FT; BLOOD-SERUM *FT; CLEARANCE *FT; PLASMA-PROTEIN *FT; BINDING *FT; LAB.ANIMAL *FT; STEREOCHEM. *FT; PHARMACOKINETICS *FT; GASTRIC-SECRETION-INHIBITORS *FT; ANTIULCERS *FT; H-K-ATPASE-INHIBITORS *FT; DM *FT
RN: 103577-45-3
FA AB; LA; CT
FS Literature

=> d 125 137 139 144 all

L5 ANSWER 125 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 2002:218580 SCISEARCH
GA The Genuine Article (R) Number: 527GP
TI Stereoselective metabolism and inhibitory effects of **lansoprazole** **enantiomers** on human liver CYPs.
AU Kim K (Reprint); Yoon Y; Cha I; Lim Y; Sohn D; Shin J
CS Inje Univ, Coll Med, Pusan, South Korea; Pusan Paik Hosp, Clin Pharmacol Ctr, Pusan, South Korea; Chonnam Natl Univ, Coll Med, Kwangju, South Korea; Soonchunhyang Univ, Coll Med, Seoul, South Korea
CYA South Korea
SO CLINICAL PHARMACOLOGY & THERAPEUTICS, (FEB 2002) Vol. 71, No. 2, pp. P98-P98.

Publisher: MOSBY, INC, 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA.
ISSN: 0009-9236.
DT Conference; Journal
LA English
REC Reference Count: 0
CC PHARMACOLOGY & PHARMACY

L5 ANSWER 137 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 96:116926 SCISEARCH
GA The Genuine Article (R) Number: TT146
TI DIRECT HPLC SEPARATION OF **ENANTIOMERS** OF PANTOPRAZOLE AND OTHER BENZIMIDAZOLE SULFOXIDES USING CELLULOSE-BASED CHIRAL STATIONARY PHASES IN REVERSED-PHASE MODE
AU TANAKA M (Reprint); YAMAZAKI H; HAKUSUI H
CS DAIICHI PHARMACEUT CO LTD, DEV RES LABS, DRUG METAB & ANALYT CHEM RES CTR, EDOGAWA KU, TOKYO 134, JAPAN (Reprint)
CYA JAPAN
SO CHIRALITY, (1995) Vol. 7, No. 8, pp. 612-615.
ISSN: 0899-0042.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 16
AB A direct, isocratic, and simple reversed-phase HPLC method was described for the separation of **enantiomers** of the proton pump inhibitor, rac-pantoprazole (PAN) using cellulose-based chiral stationary phases (Chiralcel OD-R and Chiralcel OJ-R). Some structurally related chiral benzimidazole sulfoxides, rac-omeprazole (OME) and rac-**lansoprazole** (LAN), were also studied. Chiralcel OJ-R was successful in the resolution of **enantiomers** of rac-PAN and rac-OME, while Chiralcel OD-R was most suitable for resolving the **enantiomers** of rac-LAN. Highest enantioselectivity to rac-PAN and rac-OME was achieved on Chiralcel OJ-R by using acetonitrile as an organic modifier, whereas methanol afforded better resolution of rac-LAN on Chiralcel OD-R than acetonitrile. Increases in buffer concentration and column temperature decreased retention and did not improve the resolution of the **enantiomers** on both columns. Using a mixture of 50 mM sodium perchlorate solution and acetonitrile as a mobile phase at a now rate of 0.5 ml/min, maximum separation factors of 1.26 and 1.13 were obtained for the **enantiomers** of rac-PAN and rac-OME using a Chiralcel OJ-R column, while maximum separation factor of 1.16 was obtained for the **enantiomers** of rac-LAN using a Chiralcel OD-R column. (C) 1995 Wiley-Liss, Inc.
CC PHARMACOLOGY & PHARMACY; CHEMISTRY
ST Author Keywords: **ENANTIOMERIC** SEPARATION; CHIRALCEL OD-R; CHIRALCEL OJ-R; REVERSED-PHASE HPLC; PROTON PUMP INHIBITOR; PANTOPRAZOLE; OMEPRAZOLE; **LANSOPRAZOLE**
STP KeyWords Plus (R): GASTRIC-ACID SECRETION; 1023/SK-AND-F 96022; OPTICAL RESOLUTION; ATPASE-INHIBITOR; PHARMACOKINETICS; CHROMATOGRAPHY
RF 94-1186 001; CHIRAL STATIONARY PHASES FOR HIGH-PERFORMANCE LIQUID-CHROMATOGRAPHY; IFOSFAMIDE CLINICAL PHARMACOKINETICS; ENANTIOSELECTIVE SEPARATION
RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ABOULENEIN H Y	1994	8	22	BIOMED CHROMATOGR
ALLENMARK S	1984	136	293	ANAL BIOCHEM
ALLENMARK S	1982	252	297	J CHROMATOGR
BALMER K	1994	660	269	J CHROMATOGR A
BEIL W	1992	218	265	EUR J PHARMACOL
BLIESATH H	1994	32	44	INT J CLIN PHARM TH
BUTLER B T	1992	4	155	CHIRALITY

ERLANDSSON P	1990	532	305	J CHROMATOGR-BIOMED
ISHIKAWA A	1993	16	859	J LIQ CHROMATOGR
KASHIYAMA E	1994	652	179	J CHROMATOGR B
MAELE I	1988	456	323	J CHROMATOGR
MARLE I	1991	586	233	J CHROMATOGR
PUE M A	1993	4	575	EUR J CLIN PHARMACOL
SIMON B	1990	4	373	ALIMENT PHARM THERAP
SIMON B	1990	28	443	Z GASTROENTEROL
SIMON W A	1990	39	1799	BIOCHEM PHARMACOL

L5 ANSWER 139 OF 229 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 91:627221 SCISEARCH
GA The Genuine Article (R) Number: GP144
TI EFFECTS OF THE **ENANTIOMERS** OF **LANSOPRAZOLE** (AG-1749) ON (H+ (K+)-ATPASE ACTIVITY IN CANINE GASTRIC MICROSOMES AND ACID FORMATION IN ISOLATED CANINE PARIETAL-CELLS)
AU NAGAYA H; INATOMI N; NOHARA A; SATOH H (Reprint)
CS TAKEDA CHEM IND LTD, BIOL RES LABS, DIV RES & DEV, YODOGAWA KU, 2-17-85 JUSOHONMACHI, OSAKA 532, JAPAN; TAKEDA CHEM IND LTD, PHARMACEUT PROD RES LABS, DIV RES & DEV, OSAKA 532, JAPAN
CYA JAPAN
SO BIOCHEMICAL PHARMACOLOGY, (1991) Vol. 42, No. 10, pp. 1875-1878.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 13
AB The effects of the **enantiomers** of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-sulfinyl]-1H-benzimidazole (**lansoprazole**, AG-1749) on acid formation in isolated canine parietal cells and (H+ + K+)-ATPase activity in canine gastric microsomes were investigated. Both the (+)-and the (-)-**enantiomer** of **lansoprazole** inhibited the acid formation stimulated by dibutyryl cyclic AMP (db-cAMP) in isolated canine parietal cells in a concentration-dependent manner with IC50 values of 59 and 82 nM, respectively. The **enantiomers** showed concentration-dependent inhibition of (H+ + K+)-ATPase with IC50 values of 4.2 and 5.2-mu-M, respectively. On the other hand, the IC50 values of **lansoprazole** for db-cAMP-stimulated acid formation and (H+ + K+)-ATPase were 59 nM and 2.1-mu-M, respectively. These results suggest that the two **enantiomers** of **lansoprazole** have antisecretory action due to inhibition of (H+ + K+)-ATPase.
CC PHARMACOLOGY & PHARMACY; BIOCHEMISTRY & MOLECULAR BIOLOGY
STP KeyWords Plus (R): PUMP INHIBITOR AG-1749; CANINE PARIETAL-CELLS; POSSIBLE MECHANISM; +K+)-ATPASE; GASTRIC (H+; SECRETAGOGUES; ACCUMULATION; OMEPRAZOLE
RF 91-8179 002; CANINE GASTRIC PARIETAL-CELLS; RAT STOMACH; NONSALICYLATE NONSTEROIDAL ANTIINFLAMMATORY DRUGS AUGMENT PRESTIMULATED ACID-SECRETION
RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
BERGLINDH T	1976	97	401	ACTA PHYSIOL SCAND
FINNEY D J	1964		27	STATISTICAL METHODS
FISKE C H	1925	66	375	J BIOL CHEM
FRYKLUND J	1984	33	273	BIOCHEM PHARMACOL
LOWRY O H	1951	193	265	J BIOL CHEM
NAGAYA H	1989	248	799	J PHARMACOL EXP THER
NAGAYA H	1990	252	1289	J PHARMACOL EXP THER
SATOH H	1989	248	806	J PHARMACOL EXP THER
SIGRISTNELSON K	1987	166	453	EUR J BIOCHEM
SOLL A H	1980	238	G 366	AM J PHYSIOL
SOLL A H	1978	61	370	J CLIN INVEST
WALLMARK B	1983	728	31	BIOCHIM BIOPHYS ACTA
WALLMARK B	1984	778	549	BIOCHIM BIOPHYS ACTA

L5 ANSWER 144 OF 229 TOXCENTER COPYRIGHT 2003 ACS
AN 2001:49643 TOXCENTER
DN 21150982 PubMed ID: 11256484
TI Pharmacokinetic differences between **lansoprazole enantiomers** and contribution of cytochrome P450 isoforms to enantioselective metabolism of **lansoprazole** in dogs
AU Masa K; Hamada A; Arimori K; Fujii J; Nakano M
CS Department of Pharmacy, Kumamoto University Hospital, Japan
SO BIOLOGICAL AND PHARMACEUTICAL BULLETIN, (2001 Mar) 24 (3) 274-7. Journal Code: 9311984. ISSN: 0918-6158.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
FS MEDLINE
OS MEDLINE 2001368660
LA English
ED Entered STN: 20011116
Last Updated on STN: 20011116
AB The purpose of this study was to evaluate the pharmacokinetics of **lansoprazole enantiomers** and contribution of cytochrome P450 enzymes to enantioselective metabolism in dogs. The mean Cmax and area under the curve (AUC) values of (+)-**lansoprazole** were 4-5 times greater than those of (-)-**lansoprazole** following oral administration of 30-mg racemic **lansoprazole** to dogs. The CLtot/F values of (+)-**lansoprazole** were significantly smaller than those of (-)-**lansoprazole** ($p<0.05$). The mean unbound fraction of (-)-**lansoprazole** was significantly greater than that of the (+)-**lansoprazole**. The amount of (+)-**lansoprazole** remaining was significantly greater than that of the (-)-**lansoprazole** after incubation of racemic **lansoprazole** in dog liver microsomes. When the effects of ticlopidine or ketoconazole on the metabolism of **lansoprazole** were studied using dog liver microsomes, ticlopidine significantly inhibited the formation of 5-hydroxylansoprazole, but not another metabolite, **lansoprazole** sulfone; however ketoconazole significantly inhibited formation of both metabolites. When the amount of (+)- and (-)-**enantiomers** remaining was measured in the presence and absence of ticlopidine, the amount of (+)-**lansoprazole** was significantly greater than that of the (-)-**lansoprazole**. On the other hand, there was no significant difference between the amount of (+)- and (-)-**enantiomers** remaining in combination with ketoconazole. These results suggest that the enantioselective pharmacokinetics of **lansoprazole enantiomers** are probably ascribable to their enantioselective protein binding and/or metabolism, and among the cytochrome P450 enzymes, CYP3A contributed to the enantioselective metabolism of **lansoprazole**.
CT Check Tags: Animal; In Vitro; Male
Area Under Curve
Biotransformation
*Cytochrome P-450: ME, metabolism
Dogs
Drug Interactions
*Enzyme Inhibitors: PK, pharmacokinetics
*Enzyme Inhibitors: PD, pharmacology
Half-Life
Isoenzymes: ME, metabolism
Microsomes, Liver: ME, metabolism
*Omeprazole: AA, analogs & derivatives
*Omeprazole: PK, pharmacokinetics
*Omeprazole: PD, pharmacology
Protein Binding
*Proton Pumps: AI, antagonists & inhibitors
Stereoisomerism
RN 103577-45-3 (**lansoprazole**)

73590-58-6 (Omeprazole)
9035-51-2 (Cytochrome P-450)
CN 0 (Enzyme Inhibitors); 0 (Isoenzymes); 0 (Proton Pumps)

=> d 188 all

L5 ANSWER 188 OF 229 USPATFULL
AN 2001:165896 USPATFULL
TI S-**lansoprazole** compositions and methods
IN Barberich, Timothy J., Concord, MA, United States
Yelle, William E., Billerica, MA, United States
Rubin, Paul D., Sudbury, MA, United States
PI US 2001025107 A1 20010927
AI US 2001-854065 A1 20010511 (9)
RLI Continuation of Ser. No. US 1999-240262, filed on 29 Jan 1999, PENDING
PRAI US 1998-107460P 19981105 (60)
US 1998-73141P 19980130 (60)
DT Utility
FS APPLICATION
LREP HESLIN & ROTHENBERG, PC, 5 COLUMBIA CIRCLE, ALBANY, NY, 12203
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
AB Methods and compositions are disclosed utilizing optically pure (-) **lansoprazole** for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of **lansoprazole**. The optically pure (-) isomer is also useful for the treatment of gastroesophageal reflux. (-) **Lansoprazole** is an inhibitor of H.sup.+ release and is therefore useful in the treatment of other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.

PARN CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority of U.S. provisional applications 60/073,141, filed Jan. 30, 1998, and 60/107,460, filed Nov. 5, 1998, the disclosures of which are incorporated herein by reference.

SUMM FIELD OF THE INVENTION

[0002] This invention relates to compositions of matter containing **lansoprazole**. The invention also relates to methods of treating and preventing ulcers, treating other conditions related to gastric hypersecretion, and treating psoriasis.

BACKGROUND OF THE INVENTION

[0003] Racemic **lansoprazole** is an orally active, potent, irreversible inhibitor of H.sup.+,K.sup.+-ATPase. The compound is one of the class of compounds known as gastric "proton pump" inhibitors. These compounds are weak organic bases which diffuse passively from the plasma into the acid-containing intracellular canaliculi of gastric parietal cells. At the low pH found in the lumen of these canaliculi, the protonated compounds rearrange to form pyridinium sulfenamides, which react with sulfhydryl groups present on the ATPase localized in the membranes lining the intracellular canaliculi. The alkylation of the sulfhydryl inhibits the ability of the enzyme to catalyze the secretion of H.sup.+ into the lumen in exchange for K.sup.+ ions. This inhibition results in an overall reduction in hydrochloric acid secretion by the parietal cells into the cavity of the stomach, thus increasing intragastric pH. As a consequence of reduced acidity in the stomach, the activity of the proteolytic enzyme pepsin is also markedly decreased.

Because the proton pump is the final step in acid production and the compounds of this class combine covalently with the associated H.sup.+,K.sup.+-ATPase, a profound and prolonged inhibition of gastric acid secretion can be achieved.

[0004] Proton pump inhibitors have also been reported as useful in treating psoriasis. [See PCT application WO95/18612]

[0005] The C.sub.max of racemic **lansoprazole** is at about 1.7 hours in humans and the serum half-life is about 1.5 hours, but this does not reflect the duration of the acid inhibitory effect, which is about 24 hours. Racemic **lansoprazole** is comparable to omeprazole in its effects on hepatic drug metabolizing enzyme systems.

[0006] Although no cardiovascular or obvious physical sequelae of elevated gastrin have been observed in humans on administration of racemic **lansoprazole**, fasting serum gastrin levels are significantly elevated. This is cause for concern because prolonged elevated serum gastrin appears to be associated with diffuse and focal enterochromaffin-like cell hyperplasia and focal neoplasia (carcinoids) in rats. [Larsson et al. Gastroenterology 90, 391-399 (1986)]. Thus, despite its advantages, adverse effects of racemic **lansoprazole** may remain, including, but not limited to, some incidence of hepatocellular neoplasia and gastric carcinoids on long-term therapy, and headache, diarrhea and skin alterations on acute therapy. There has also been some concern about the inhibition of cytochrome P450 enzymes by racemic **lansoprazole** [Kromer Digestion 56, 443-454 (1995)]; this effect would lead to adverse drug-drug interactions.

[0007] The following adverse events have been reported in **lansoprazole**-treated patients: Body as a Whole - asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise; Cardiovascular System--angina, cereborvascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation; Digestive System--melena, anorexia, bezoar, cardiospasm, cholelithiasis, constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis, vomiting; Endocrine System--diabetes mellitus, goiter, hyperglycemia/hypoglycemia, Hematologic and Lymphatis System--anemia, hemolysis; Metabolic and Nutritional Disorders--gout, weight gain/loss; Musculoskeletal System--arthritis/arthralgia, musculoskeletal pain, myalgia; Nervous System--agitation, amnesia, anxiety, apathy, confusion, depression, dizziness/syncope, hallucinations, hemiplegia, aggravated hostility, decreased libido, nervousness, paresthesia, thinking abnormality; Respiratory System--asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, pneumonia, upper respiratory inflammation/infection; Skin and Appendages--acne, alopecia, pruritis, rash, urticaria, Special Senses--amblyopia, deafness, eye pain, visual field defect, otitis media, taste perversion, tinnitus; Urogenital System--abnormal menses, albuminuria, breast enlargement/gynecomastia, breast tenderness, glycosuria, hematuria, impotence, kidney calculus.

[0008] It would therefore be particularly desirable to find a compound with the advantages of the racemic mixture of **lansoprazole** which would not have the aforementioned disadvantages.

SUMMARY OF THE INVENTION

[0009] This invention relates to the use of optically pure S(-)

lansoprazole for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, and other disorders including those that would benefit from an inhibitory action on gastric acid secretion. S(-)**Lansoprazole** inhibits the H.sup.+, K.sup.+-ATPase associated with the gastric proton pump and the resulting secretion of gastric acid by parietal cells providing therapy in diseases associated with gastric hyperacidity. The invention also relates to a method of treating psoriasis using optically pure S(-) **lansoprazole**. Optically pure (-) **lansoprazole** provides this treatment while substantially reducing adverse effects, including, but not limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric neoplasms or carcinoids, headache, diarrhea and skin alterations which are associated with the administration of the racemic mixture of **lansoprazole**.

[0010] The invention also relates to certain oral pharmaceutical compositions containing the S(-) isomer of **lansoprazole**.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The active compound of these compositions and methods is an optical isomer of **lansoprazole**. The preparation of racemic **lansoprazole** is described in U.S. Pat. Nos. 4,628,098 and 4,689,333. The medicinal chemistry and clinical aspects of racemic **lansoprazole** have been reviewed by Garnett [Ann. Pharmacother. 30, 1425-1436 (1996)], by Langtry and Wilde [Drugs 54, 473-500 1997)] and by Barradell et al. [Drugs 44, 225-250(1992)]. Chemically, the active compound is the (-) isomer of 2-[3-methyl-4-(2, 2, 2-trifluoroethoxy)pyrid-2-yl] methylsulfinyl-benzimidazole(I), hereinafter referred to as **lansoprazole**. ##STR1##

[0012] (-) **Lansoprazole**, which is the subject of the present invention, is not presently commercially available; only the 1:1 racemic mixture is commercially available as Prevacid.RTM..

[0013] Syntheses of R (+) **lansoprazole** and S(-) **lansoprazole** by asymmetric oxidation and by bioreduction are described in PCT applications WO 9602535 and 9617077, respectively, the disclosures of which are incorporated herein by reference. The enrichment of-single **enantiomers** by crystallization of the racemate from non-racemic mixtures is described in PCT application WO 97/02261, the disclosure of which is also incorporated herein by reference.

[0014] The pharmacology of the individual **enantiomers** in canine parietal cells and gastric microsomes has been reported by Nagaya et al. [Biochem. Pharmacol. 42, 1875-1878 (1991)], who concluded that "the effects of the (+) and (-) **enantiomer** of **lansoprazole** on acid formation stimulated by db-cAMP in isolated parietal cells were almost identical." Similarly, inhibition of ATPase activity in gastric microsomes by the two **enantiomers** did not differ significantly over the range of concentrations tested.

[0015] It has now been discovered that the optically pure (-) isomer of **lansoprazole** is a superior agent for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, psoriasis and other disorders, including those that would benefit from an inhibitory action on H.sup.+,K.sup.+-ATPase in that it provides this effective treatment while substantially reducing the adverse effects of racemic **lansoprazole** including, but not limited to, hepatocellular neoplasia, gastric carcinoids, headache, diarrhea and skin alterations. The S(-) isomer of **lansoprazole** is also a superior agent for treating ulcers and other disorders by virtue of its lessened liability

for drug-drug interactions and its greater predictability of dosage among patients, as discussed below. Surprisingly, it also shows a longer duration, a higher AUC (area under the curve--a composite measure of efficacy and duration), and a more rapid onset as a result of lower first pass metabolism.

[0016] The present invention encompasses a method of treating ulcers, which comprises administering to a human in need of such therapy, an amount of (-) **lansoprazole**, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate the symptoms of ulcers. The method substantially reduces the concomitant liability of adverse effects associated with the administration of the racemic compound by providing an amount which is insufficient to cause the adverse effects associated with the racemic mixture of **lansoprazole**.

[0017] The present invention also encompasses an oral antiulcer composition for the treatment of a human in need of antiulcer therapy, which comprises a pharmaceutically acceptable carrier for oral administration and a therapeutically effective amount of (-) **lansoprazole**, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer. Preferably the composition is in the form of a tablet or capsule and the amount of (-) **lansoprazole** in the tablet or capsule is 15, 30 or 60 mg.

[0018] The present invention further encompasses a method of treating gastroesophageal reflux disease and of treating conditions caused by or contributed to by gastric hypersecretion. Conditions associated with hypersecretion in humans may include, but are not limited to, Zollinger-Ellison syndrome.

[0019] The present invention further encompasses a method of treating psoriasis while substantially reducing the adverse effects of racemic **lansoprazole**.

[0020] Utilizing the optically pure or substantially optically pure isomer of (-) **lansoprazole** results in enhanced efficacy, diminished adverse effects, and accordingly, an improved therapeutic index. It also provides more rapid onset and longer duration of the therapeutic effect. Moreover, the S(-) **enantiomer** exhibits fewer drug-drug interactions and shows less variation in the patient population between so-called good metabolizers and poor metabolizers. It is therefore, more desirable to use the (-) isomer of **lansoprazole** than to administer the racemic mixture because predictability of an effective and safe dose for an individual patient is greater. The S(-) **enantiomer** of **lansoprazole** is metabolized by both CYP2D6 and CYP3A4; the R(+) **enantiomer** is metabolized only by CYP2D6, which is the polymorphically expressed enzyme. Because it is metabolized by both enzymes, the S(-) shows less variability in the patient population and a more predictable dosage regimen. Surprisingly, the S-(-) isomer also shows a longer duration, a higher AUC and a more rapid onset as a result of lower first pass metabolism.

[0021] The term "adverse effects" includes, but is not limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric carcinoids, headache, diarrhea, skin alterations and drug-drug interactions.

[0022] The term "substantially free of its (+) stereoisomer" as used herein means that the compositions contain at least 90% by weight of (-) **lansoprazole** and 10% by weight or less of (+) **lansoprazole**. In a more preferred embodiment the term "substantially free of the (+) isomer" means that the composition contains at least 99% by weight of (-) **lansoprazole**, and 1% or

less of (+) **lansoprazole**. These percentages are based upon the total amount of **lansoprazole** in the composition. The terms "substantially optically pure (-) isomer of **lansoprazole**" or "substantially optically pure (-) **lansoprazole**" and "optically pure (-) isomer of **lansoprazole**" and "optically pure (-) **lansoprazole**" are also encompassed by the above-described amounts.

[0023] The term "treating ulcers" as used herein means treating, alleviating or palliating such conditions, and thus providing relief from the symptoms of nausea, heartburn, post-prandial pain, vomiting, and diarrhea.

[0024] The term "a method for treating gastroesophageal reflux diseases in a human" as used herein means treating, alleviating or palliating the conditions that result from the backward flow of the stomach contents into the esophagus.

[0025] The term "treating a condition caused, or contributed to, by gastric hypersecretion in a human" as used herein means treating, alleviating or palliating such disorders associated with hypersecretion, thus providing relief from the symptoms of the aforementioned conditions. Zollinger-Ellison Syndrome is among the conditions caused by or contributed to by hypersecretion.

[0026] The term "treating psoriasis" as used herein means treating, alleviating or palliating the condition, and thus providing relief from the symptoms of pruritis, epidermal scaling, itching and burning.

[0027] The magnitude of a prophylactic or therapeutic dose of (-) **lansoprazole** in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for (-) **lansoprazole** for the conditions described herein is from about 10 mg to about 180 mg in single or divided doses. Preferably a daily dose range should be about 15 mg to about 60 mg in single or divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 10 mg to about 15 mg and increased up to about 60 mg or higher depending on the patient's global response. It is further recommended that children and patients over 65 years and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "an amount sufficient to alleviate or palliate ulcers but insufficient to cause said adverse effects," "an amount sufficient to alleviate the symptoms of gastroesophageal reflux but insufficient to cause said adverse effects," "an amount sufficient to alleviate gastric hypersecretion but insufficient to cause said adverse effects" and "an amount sufficient to treat psoriasis" are encompassed by the above-described dosage amounts and dose frequency schedule.

[0028] The relative activity, potency and specificity of optically pure **lansoprazole** and racemic **lansoprazole** both as gastric antisecretory agents and plasma gastrin elevating agents can be determined by a pharmacological study in animals according to the method of Decktor et al. [J. Pharmacol. Exp. Ther. 249, 1-5 (1989)]. The test provides an estimate of relative activity, potency and, through a measure of specificity, an estimate of therapeutic index. Fasted rats,

implanted with a gastric cannula, receive single oral or parenteral doses of (+) **lansoprazole**, (-) **lansoprazole** or racemate, 1 hour before collection of gastric juice over a four hour period. Acid output and pH are then determined on each sample. Dose response evaluations are performed with each compound to determine the lowest dose which inhibits acid output by at least 95% and maintains gastric pH above 7.0. Plasma gastrin levels are then determined in a second group of rats treated with the doses selected in the first series of tests. Blood samples are taken for analyses over the five hour period after dosing, and both peak level as well as area-under-the-curve analyses of the gastrin responses are made. These responses are then analyzed statistically using Student's "t" test to assess whether equivalent antisecretory doses show differences in gastrin responses.

[0029] Any suitable route of administration may be employed for providing the patient with an effective dosage of (-) **lansoprazole**. Rectal, parenteral (subcutaneous, intramuscular, intravenous) transdermal, topical and like forms of administration are possible; oral administration is preferred. Oral dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, and the like.

[0030] The pharmaceutical compositions of the present invention comprise (-)**lansoprazole** as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

[0031] The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic bases. Since the compound of the present invention is a weak acid and is unstable at low pH, salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic and organic bases. Suitable pharmaceutically acceptable base addition salts for the compound of the present invention include metallic salts of aluminum, calcium, lithium, magnesium, potassium, sodium, titanium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. If any salt is to be used, sodium salts are preferred.

[0032] The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations. It has been found that the inclusion of basic salts of calcium and magnesium in the compositions allows the preparation of tablets and capsules having **lansoprazole** in a non-salt form and yet retaining good stability. If desired, tablets and granules may be coated by standard aqueous or nonaqueous techniques. Oral dosage forms suitable for **lansoprazole** are described in U.S. Pat. No. 5,035,899 and in PCT applications WO96/01624, WO97/12580 and WO97/25030, the disclosures of which are incorporated herein by reference.

[0033] In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release formulations, which are well known in the art. Compositions suitable for rectal administration are described in European Application 645140, the disclosure of which is incorporated herein by reference.

[0034] Pharmaceutical compositions of the present invention suitable for

oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

[0035] For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 5 mg to about 180 mg of the active ingredient, and each cachet or capsule contains from about 5 mg to about 180 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains one of three dosages: about 15 mg, about 30 mg or about 60 mg of (-) **lansoprazole** for oral administration.

[0036] The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

DETD EXAMPLES

Example 1--Tablets

[0037]

Composition per tablet:

S(-) **lansoprazole**	30	mg
Precipitated calcium carbonate	50	mg
Corn Starch	40	mg
Lactose	73.4	mg
Hydroxypropylcellulose	6	mg
Magnesium stearate	(0.05	ml)
Total	200.0	mg

EXAMPLE 1

[0038] S(-) **Lansoprazole**, precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose are mixed together, water is added, and the mixture is kneaded, then dried in vacuum at 40.degree. C. for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this is added magnesium stearate and the resultant mixture is made up into tablets each weighing 200 mg on a rotary tableting machine.

Example 2--Granules

[0039]

Composition per tablet:

S(-) **lansoprazole**	30	mg
Magnesium carbonate	20	mg
Corn Starch	80	mg
Microcrystalline cellulose	20	mg
Carboxymethylcellulose calcium	10	mg
Hydroxypropylcellulose	10	mg
Pluronic F68	4	mg
Lactose	26	mg
Water	(0.05	ml)
Total	200	mg

EXAMPLE 2

[0040] The ingredients above are mixed well in the proportions shown, water is added, and the mixture is kneaded and granulated in an extruder granulator (screen size 1.0 mm .phi.). The granules are immediately converted to spherical form in a spheronizer. The spherical granules are then dried under vacuum at 40.degree. C. for 16 hours and passed through round sieves to give 12- to 42-mesh granules.

Example 3--Capsules

[0041]

Enteric coating composition:		
Eudragit L-30D	138	mg (solids 41.4 mg)
Talc	4.1	mg
Polyethylene glycol 5000	12.4	mg
Tween 80	2.1	mg
Water	276	.mu.l
Composition of enteric granules:		
Granules of Example 5	200	mg
Enteric coat	60	mg
Total	260	mg
Composition per capsule:		
Enteric granules	260	mg
No. 1 hard capsule	76	mg
Total	336	mg

EXAMPLE 3

[0042] Enteric granules are produced by coating the granules obtained in Example 2 with the enteric coating composition shown using a fluidized bed granulator under conditions such that the inlet air temperature is 50.degree. C. and the granule temperature is about 40.degree. C. Number 1 hard capsules are filled with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine.

[0043] Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet. An enteric coating, such as the polyacrylate Eudragit L.RTM. and Eudragit S.RTM. series, is applied by spray coating the tablets, preferably with an aqueous dispersion of the coating polymer.

CLM What is claimed is:

1. A method of treating ulcers with **lansoprazole** which comprises administering to a human a therapeutically effective amount of optically pure S(-)isomer of **lansoprazole**, or a pharmaceutically acceptable salt thereof.

2. A method of treating gastroesophageal reflux disease which comprises administering to a human a therapeutically effective amount of optically pure S(-)isomer of **lansoprazole**, or a pharmaceutically acceptable salt thereof.

3. A method of treating a condition caused by or contributed to by gastric hypersecretion which comprises administering to a human a therapeutically effective amount of optically pure S(-)isomer of **lansoprazole**, or a pharmaceutically acceptable salt thereof.

4. The method according to claim 3 wherein said condition is Zollinger-Ellison Syndrome.

5. A method of treating psoriasis which comprises administering to a human a therapeutically effective amount of optically pure S(-)isomer of **lansoprazole**, or a pharmaceutically acceptable salt thereof.

6. The method of any of claims 1-5 wherein (-) **lansoprazole** is administered orally.

7. The method of claim 6 wherein the amount of (-) **lansoprazole** or a pharmaceutically acceptable salt thereof administered is from about 5 mg to about 180 mg per day.

8. The method of claim 7 wherein the amount administered is from about 10 mg to about 60 mg per day.

9. The method of any of claims 1-5 wherein the amount of (-) **lansoprazole** or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of **lansoprazole**.

10. The method of any of claims 1-5 wherein the amount of (-) **lansoprazole** or a pharmaceutically acceptable salt thereof is greater than approximately 99% by weight of the total weight of **lansoprazole**.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier for oral therapy and a therapeutically effective amount of (-) **lansoprazole** or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

12. A pharmaceutical composition according to claim 11 in the form of a tablet or capsule.

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NCL NCLM: 546/273.700
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IC [7]
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PASSWORD:
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L1 4051 S LANSOPRAZOLE/CN
L2 14922 S LANSOPRAZOLE
L3 14 S -LANSAPRAZOLE
L4 217807 S ENANTIOMER?
L5 229 S L2 AND L4
SAVE L5 B854085/A

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L5 ANSWER 1 OF 229 ADISCTI COPYRIGHT 2003 (ADIS)
AN 1999:1505 ADISCTI
DN 800732011
TI Pharmacokinetic differences between **lansoprazole enantiomers** in rats.
AU Arimori K; Yasuda K; Katsuki H; et al.
SO Journal of Pharmacy and Pharmacology (Nov 1, 1998), Vol. 50, pp. 1241-1245
DT Citation
RE Peptic Ulcer Disease
FS Citation
LA English
CT Drug Descriptors: **Lansoprazole**, pharmacokinetics; Antisecretories, pharmacokinetics; Antiulcers, pharmacokinetics; ATPase inhibitors, pharmacokinetics; Enzyme inhibitors, pharmacokinetics; Gastric antisecretories, pharmacokinetics; General pump inhibitors, pharmacokinetics; Proton pump inhibitors, pharmacokinetics
CT Other Descriptors: **Enantiomers**; Clinical pharmacokinetics

L5 ANSWER 2 OF 229 ADISCTI COPYRIGHT 2003 (ADIS)
AN 1996:57315 ADISCTI
DN 800438292

TI Determination of R(+)- and S(-)-**lansoprazole** using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans.
AU Katsuki H; Yagi H; Arimori K; et al.
SO Pharmaceutical Research (Apr 1, 1996), Vol. 13, pp. 611-615
DT Citation
RE Peptic Ulcer Disease
FS Citation
LA English
CT Drug Descriptors: **Lansoprazole**, pharmacokinetics; Antisecretories, pharmacokinetics; Antiulcers, pharmacokinetics; ATPase inhibitors, pharmacokinetics; Enzyme inhibitors, pharmacokinetics; Gastric antisecretories, pharmacokinetics; General pump inhibitors, pharmacokinetics; Proton pump inhibitors, pharmacokinetics
CT Other Descriptors: Clinical pharmacokinetics; **Enantiomers**

L5 ANSWER 3 OF 229 ADISCTI COPYRIGHT 2003 (ADIS)
AN 1992:52427 ADISCTI
DN 800166103
TI An enantioselective HPLC method for the determination of optical isomers of **lansoprazole** in human plasma.
AU El Shourbagy T; Elger R S; Chu S y.
SO Pharmaceutical Research (Oct 1, 1992), Vol. 9 (Suppl.), pp. 16
DT Citation
RE Peptic Ulcer Disease
FS Citation
LA English
CT Drug Descriptors: **Lansoprazole**, pharmacokinetics; Antisecretories, pharmacokinetics; Antiulcers, pharmacokinetics; ATPase inhibitors, pharmacokinetics; Enzyme inhibitors, pharmacokinetics; Gastric antisecretories, pharmacokinetics; General pump inhibitors, pharmacokinetics; Proton pump inhibitors, pharmacokinetics
CT Other Descriptors: **Enantiomers**; Clinical pharmacokinetics

L5 ANSWER 4 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:602410 BIOSIS
DN PREV200200602410
TI Restoration of acid secretion following treatment with proton pump inhibitors.
AU Shin, Jai Moo; Sachs, George (1)
CS (1) Membrane Biology Laboratory, West Los Angeles VA Medical Center, 11301 Wilshire Boulevard, Building 113, Room 324, Los Angeles, CA, 90073: gsachs@ucla.edu USA
SO Gastroenterology, (November, 2002) Vol. 123, No. 5, pp. 1588-1597. http://www.gastrojournal.org/. print. ISSN: 0016-5085.
DT Article
LA English
AB Background & Aims: Proton pump inhibitors (PPIs) are covalent inhibitors of the gastric H+,K+-adenosine triphosphatase (ATPase) forming disulfide bonds. Recovery of acid secretion after PPI inhibition may be due to de novo synthesis of pump protein and/or disulfide reduction and reactivation of inhibited pump. The half-time of recovery of acid secretion in rats following omeprazole treatment is apprx15 hours, whereas pump protein half-life is 54 hours. In humans, the half-life of the inhibitory effect on acid secretion is apprx28 hours for omeprazole and apprx46 hours for pantoprazole. Whereas all PPIs bind to cysteine 813, pantoprazole additionally binds to cysteine 822, deeper in the membrane domain of TM6. Their different durations of action may reflect different rates of pump reactivation due to differing accessibility of the disulfides to glutathione. Methods: Rats were stimulated and treated with 30 mg/kg of each PPI. Gastric ATPase was prepared and reversal of inhibition of the H+,K+-ATPase was measured as the time-dependent restoration of activity by incubation with dithiothreitol or glutathione. Results: One hundred

percent reactivation of ATPase following inhibition in vivo by omeprazole or its **enantiomers** was seen with dithiothreitol and 89% with glutathione. Similar data were found for **lansoprazole** or rabeprazole. No reactivation by either reducing agent was seen following inhibition by pantoprazole. Conclusions: Recovery of acid secretion following inhibition by all PPIs, other than pantoprazole, may depend on both protein turnover and reversal of the inhibitory disulfide bond. In contrast, recovery of acid secretion after pantoprazole may depend entirely on new protein synthesis.

CC Biophysics - Membrane Phenomena *10508
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014

BC Hominidae 86215

IT Major Concepts
Gastroenterology (Human Medicine, Medical Sciences); Membranes (Cell Biology); Pharmacology

IT Chemicals & Biochemicals
dithiothreitol; esomeprazole: enzyme inhibitor - drug, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics; gastric acid proton pump protein: de novo synthesis, inhibition, reactivation, secretion recovery; glutathione; **lansoprazole**: enzyme inhibitor - drug, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics; pantoprazole: enzyme inhibitor - drug, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics; proton pump inhibitor: enzyme inhibitor - drug, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics; proton,potassium ion-ATPase; rabeprazole: enzyme inhibitor - drug, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): patient

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 3483-12-3 (DITHIOTHREITOL)
119141-88-7 (ESOMEPRAZOLE)
70-18-8 (GLUTATHIONE)
103577-45-3 (**LANSOPRAZOLE**)
102625-70-7 (PANTOPRAZOLE)
117976-89-3 (RABEPRAZOLE)

L5 ANSWER 5 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:510349 BIOSIS
DN PREV200200510349
TI Application of pharmaceutical principles to clinical practices.
AU Nakano, Masahiro (1)
CS (1) Department of Clinical Pharmaceutics, Division of Clinical Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka, 422-8526 Japan
SO Yakuzaigaku, (June, 2002) Vol. 62, No. 2, pp. 45-57. print.
ISSN: 0372-7629.
DT General Review
LA English
AB The author believes that a supply of new preparations and studies on the disposition of drugs in patients with various physiological and pathological conditions are required to develop new drug therapy. Therefore these are considered to be the responsibility of pharmacists in so-called special function hospitals, such as university hospitals and

national center hospitals. Works related to clinical drug therapy carried out at the Department of Pharmacy, Kumamoto University Hospital, are described. The topics related to drug delivery include injections containing anticancer drugs for intra-arterial administration, lidocaine gels for dermal anesthesia, glucagon solution for nasal administration and midazolam solution for sublingual administration. The topics related to the disposition of drugs include clinical pharmacokinetic studies, medical uses of adsorbents and evaluations of sustained release formulations.

CC Biochemical Studies - General *10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Pathology, General and Miscellaneous - Therapy *12512
Dental and Oral Biology - Physiology and Biochemistry *19004
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Cardiovascular System *22010
Pharmacology - Immunological Processes and Allergy *22018
Pharmacology - Neuropharmacology *22024
Toxicology - General; Methods and Experimental *22501
Toxicology - Pharmacological Toxicology *22504
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008

BC Hominidae 86215

IT Major Concepts
Pharmacology

IT Parts, Structures, & Systems of Organisms
saliva: dental and oral system

IT Diseases
drug overdose: toxicity

IT Chemicals & Biochemicals
5-fluoro-2-deoxyuridine derivative; aclarubicin: antineoplastic - drug; adsorbents: medical uses; anticancer drugs: intra-arterial administration; cefmenoxine; cisplatin: antineoplastic - drug; disopyramide; famotidine: antihistamine - drug, histamine H2-receptor antagonist - drug; glucagon: enzyme inhibitor - drug, nasal administration, solution formulation; **lansoprazole**; lidocaine: gel formulation, local anesthetic - drug; midazolam: solution formulation, sublingual administration; nicardipine: calcium channel blocker - drug, cardiovascular - drug; phenobarbital; roxatidine; theophylline: autonomic - drug, enzyme inhibitor - drug, sustained release formulation

IT Methods & Equipment
activated carbon beads: medical equipment; dermal anesthesia: anesthesia method; drug delivery: drug delivery method; drug therapy: new, therapeutic method; gastrointestinal dialysis: therapeutic method; stereoselective analysis: analytical method

IT Miscellaneous Descriptors
clinical pharmacokinetics studies; clinical practices; drug disposition; drug interactions; **enantiomers**; genetic polymorphisms; national center hospitals; pathological conditions; pharmaceutical principles; pharmacist responsibilities; physiological conditions; special function hospitals; sustained release drug formulations; university hospitals

CO Kumamoto University Hospital

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): patient

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 57576-44-0 (ACLARUBICIN)
15663-27-1 (CISPLATIN)
3737-09-5 (DISOPYRAMIDE)
76824-35-6 (FAMOTIDINE)
9007-92-5 (GLUCAGON)

103577-45-3 (**LANSOPRAZOLE**)
137-58-6 (LIDOCAINE)
59467-70-8 (MIDAZOLAM)
55985-32-5 (NICARDIPINE)
50-06-6 (PHENOBARBITAL)
78273-80-0 (ROXATIDINE)
58-55-9 (THEOPHYLLINE)

L5 ANSWER 6 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:463979 BIOSIS
DN PREV200200463979
TI Enantioselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.
AU Kim, Kyoung-Ah; Shon, Ji-Hong; Park, Ji-Young; Yoon, Young-Ran; Kim, Min-Jung; Yun, Doo-Hee; Kim, Moon-Kyung; Cha, In-June; Hyun, Myung-Ho; Shin, Jae-Gook (1)
CS (1) Clinical Pharmacology Center, Pusan Paik Hospital, Inje University College of Medicine, 633-165, Kaekum-Dong, Jin-Ku, Pusan, 614-735: phshinjg@ijnc.inje.ac.kr South Korea
SO Clinical Pharmacology & Therapeutics, (July, 2002) Vol. 72, No. 1, pp. 90-99. http://www.mosby.com/cpt. print.
ISSN: 0009-9236.
DT Article
LA English
AB Objective: To evaluate the enantioselective disposition of **lansoprazole** in relation to the genetic polymorphism of CYP2C19. Methods: A single oral dose of racemic **lansoprazole** (30 mg) was administered to 6 extensive metabolizers and 6 poor metabolizers whose genotypes were determined by use of polymerase chain reaction-restriction fragment length polymorphism. The pharmacokinetic parameters were estimated from the plasma concentrations of **lansoprazole** racemate, its **enantiomers**, and metabolites, which were measured for 24 hours after drug administration. The unbound fraction of **lansoprazole enantiomers** was determined by means of ultrafiltration of fresh human serum spiked with racemic **lansoprazole**. Results: The plasma concentrations of R(+)-**lansoprazole** were consistently higher than those of the S(-)-**enantiomer** in both extensive and poor metabolizers of CYP2C19, and the mean area under the plasma concentration-time curve of the (+)- and (-)-**enantiomers** showed 4.3- and 5.8-fold differences between poor and extensive metabolizers, respectively. The (+)/(-) ratios of **lansoprazole** clearance were not significantly different between poor and extensive metabolizers (0.19 +- 0.07 and 0.05 +- 0.08, respectively). The values for volume of distribution of the (-)-**enantiomer** were 3- and 10-fold greater, respectively, than those of the (+)-**enantiomer** in poor and extensive metabolizers, which was related to a 2-fold higher unbound fraction of the (-)-**enantiomer**. Conclusions: The effect of CYP2C19 genetic polymorphism on the enantioselective disposition of **lansoprazole** seems to be less significant than the effect on omeprazole and pantoprazole. The disposition of **lansoprazole** **enantiomers** appears to be influenced by enantioselective protein binding and by enantioselective metabolism of **lansoprazole**.
CC Genetics and Cytogenetics - General *03502
Genetics and Cytogenetics - Human *03508
Genetics and Cytogenetics - Population Genetics *03509
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Pharmacology - General *22002

Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014
BC Hominidae 86215
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; Population Genetics (Population Studies)
IT Parts, Structures, & Systems of Organisms
plasma: blood and lymphatics
IT Chemicals & Biochemicals
cytochrome P4502C19 [CYP2C19]: metabolism; **lansoprazole**: enantioselective disposition, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacokinetics
IT Methods & Equipment
polymerase chain reaction-restriction fragment length polymorphism: genetic method; ultrafiltration: filtration, isolation method
IT Miscellaneous Descriptors
pharmacogenetics
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 330589-90-7 (CYTOCHROME P4502C19)
103577-45-3 (**LANSOPRAZOLE**)

L5 ANSWER 7 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:227645 BIOSIS
DN PREV200200227645
TI Stereoselective disposition of **lansoprazole** in extensive and poor metabolizers of CYP2C19.
AU Shin, J. (1); Kim, K. (1); Shon, J. (1); Park, J. (1); Yun, D. (1); Cha, I. (1)
CS (1) Coll. of Med., Inje Univ., Pusan Paik Hosp., Pusan South Korea
SO Clinical Pharmacology & Therapeutics, (February, 2002) Vol. 71, No. 2, pp. P98. print.
Meeting Info.: Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics Atlanta, Georgia, USA March 24-27, 2002
ISSN: 0009-9236.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Genetics and Cytogenetics - Human *03508
Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014
BC Hominidae 86215
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Medical Genetics (Allied Medical Sciences); Pharmacology
IT Parts, Structures, & Systems of Organisms
plasma: blood and lymphatics
IT Chemicals & Biochemicals
CYP2C19; **lansoprazole: enantiomers**, gastrointestinal - drug, oral administration, stereoselective disposition

IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 103577-45-3 (**LANSOPRAZOLE**)
GEN human CYP2C19 gene (Hominidae): polymorphism

L5 ANSWER 8 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:227644 BIOSIS
DN PREV200200227644
TI Stereoselective metabolism and inhibitory effects of **lansoprazole enantiomers** on human liver CYPS.
AU Kim, K. (1); Yoon, Y.; Cha, I.; Lim, Y.; Sohn, D.; Shin, J.
CS (1) Coll. of Med., Inje Univ., Pusan Paik Hosp., Pusan South Korea
SO Clinical Pharmacology & Therapeutics, (February, 2002) Vol. 71, No. 2, pp. P98. print.
Meeting Info.: Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics Atlanta, Georgia, USA March 24-27, 2002
ISSN: 0009-9236.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Physiology and Biochemistry *14004
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014
BC Hominidae 86215
IT Major Concepts
Digestive System (Ingestion and Assimilation); Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Parts, Structures, & Systems of Organisms
liver microsomes: digestive system
IT Chemicals & Biochemicals
CYP2C19: inhibition; CYP2C9; CYP3A4; S-mephenytoin; **lansoprazole: enantiomers**, gastrointestinal - drug, stereoselective inhibitory effects, stereoselective metabolism
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 329978-01-0 (CYP2C9)
70989-04-7 (S-MEPHENYTOIN)
103577-45-3 (**LANSOPRAZOLE**)

L5 ANSWER 9 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:139897 BIOSIS
DN PREV200200139897
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of **lansoprazole** by human liver microsomes.
AU Katsuki, H.; Hamada, A.; Nakamura, C.; Arimori, K.; Nakano, M. (1)
CS (1) Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto, 860-8556: nakano@kaiju.medic.kumamoto-u.ac.jp Japan
SO European Journal of Clinical Pharmacology, (December, 2001) Vol. 57, No.

10, pp. 709-715. print.
ISSN: 0031-6970.

DT Article

LA English

AB Objective: The aim of this investigation was to clarify the stereoselective properties in **lansoprazole** metabolism by monitoring the metabolic consumption for each **enantiomer** and the formation of the main metabolites, **lansoprazole** sulfone and 5-hydroxylansoprazole, in the presence of human liver microsomal enzymes. Methods: Human liver microsomes or recombinant cytochrome P450 (CYP) enzymes were incubated with either (+-)-, (+)-, or (-)-**lansoprazole** in the presence of reduced nicotinamide adenine dinucleotide phosphate. The metabolic consumption of **lansoprazole enantiomers** was estimated from the amounts of **enantiomers** consumed by microsomal enzymes after incubation at 37degreeC for 60 min. Metabolites of **lansoprazole, lansoprazole** sulfone, and 5-hydroxylansoprazole were determined after incubation at 37degreeC for 20 min, and kinetic parameters (Michaelis constant (Km) and maximum velocity (Vmax)) were obtained using Eadie-Hofstee plots. Results: (-)-**Lansoprazole** was metabolized more preferentially than (+)-**lansoprazole** in human liver microsomes. Stereoselective sulfoxidation ((-)>(+)) and hydroxylation ((+)>(-)) were observed in human liver microsomes. Strikingly, in sulfoxidation, a significantly higher intrinsic clearance (Vmax,1/Km,1) of (-)-**lansoprazole** (0.023 +- 0.001 ml/min/mg) than (+)-**lansoprazole** (0.006 +- 0.000 ml/min/mg) was observed. Consequently, sulfoxidation is likely to play an important role in the stereoselective metabolism of **lansoprazole enantiomers**. P450-isoform specificity for each **enantiomer** was evident. CYP3A4, which mainly catalyzed sulfoxidation, was more active toward (-)-**lansoprazole** in either a chiral or racemic drug as a substrate, CYP2C19, which catalyzed hydroxylation, preferentially metabolized (+)-**lansoprazole**. The consumption of (+)-**lansoprazole** was markedly inhibited by (-)-**lansoprazole**, indicating a metabolic **enantiomer/enantiomer** interaction. However, this alteration of recombinant CYP2C19 specificity for (+)-**lansoprazole** did not appear in metabolism in human liver microsomes. Conclusions: Stereoselective metabolism was observed in human liver microsomes, and this stereoselectivity was mainly based on CYP3A4 specificity for preferable metabolism of (-)-**lansoprazole**.

CC Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Digestive System - Physiology and Biochemistry *14004
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014

BC Hominidae 86215

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Pharmacology

IT Parts, Structures, & Systems of Organisms
liver microsomes: digestive system

IT Chemicals & Biochemicals
5-hydroxylansoprazole; cytochrome P-450 2C19; cytochrome P-450 3A4; dextro-**lansoprazole**: gastric secretion inhibitor - drug, gastrointestinal - drug, metabolism; **lansoprazole** sulfone; levo-**lansoprazole**: gastric secretion inhibitor - drug, gastrointestinal - drug, metabolism; racemic-**lansoprazole**: gastric secretion inhibitor - drug, gastrointestinal - drug, metabolism

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms

Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 131926-98-2 (5-HYDROXYLANSOPRAZOLE)
330589-90-7 (CYTOCHROME P-450 2C19)
329736-03-0 (CYTOCHROME P-450 3A4)
138530-94-6 (DEXTRO-**LANSOPRAZOLE**)
131926-99-3 (**LANSOPRAZOLE** SULFONE)
138530-95-7 (LEVO-**LANSOPRAZOLE**)
103577-45-3 (RACEMIC-**LANSOPRAZOLE**)

L5 ANSWER 10 OF 229 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:26665 BIOSIS
DN PREV200200026665
TI Relative efficacies of gastric proton-pump inhibitors on a milligram basis: Desired and undesired SH reactions. Impact of chirality.
AU Kromer, W. (1)
CS (1) Dept. of Pharmacology, Byk Gulden, Byk-Gulden-Str. 2, D-78467, Konstanz Germany
SO Scandinavian Journal of Gastroenterology, (2001) Vol. 36, No. Supplement 234, pp. 3-9. print.
ISSN: 0036-5521.
DT Article
LA English
AB Gastric proton-pump inhibitors (PPIs) are prodrugs. Their acid activation at pH 1.0 inside the canaliculus of a parietal cell should be fast relative to their serum elimination rate. Actually, all PPIs display chemical activation half-lives at pH 1.0 of a few minutes at the most, while being eliminated from serum with a half-life of about 1 h. This is the main reason they show similar antisecretory efficacies on a milligram basis. It is in line with about 5% to 15% higher healing rates in GERD, DU and GU when 40 mg is compared to 20 mg of either omeprazole or pantoprazole. The comparably large biological variation between patient samples explains why some studies show statistically significant differences between the two doses, while others do not. However, it would matter to the individual patient if s/he was the one additionally healed by a 40 mg dose within a defined treatment period. Chemical activation of PPI prodrugs is unwanted in weakly acidic tissue compartments such as lysosomes or secretory granules. However, the ratio of the serum elimination half-life (availability at the target) to the chemical activation half-life at a critical pH 5.0 is reversed only with pantoprazole, when compared to pH 1.0 (i.e. the ratio is <1 at pH 5.0 and >1.0 at pH 1.0). This is the basis of the high pH selectivity of pantoprazole. In contrast, rabeprazole is activated at pH 5.0 almost as quickly as it is at pH 1.0 and much faster than it is eliminated from serum. This unwanted reactivity of rabeprazole at pH 5.0 does not contribute to the antisecretory action at pH 1.0 and results in poor pH selectivity. Omeprazole and **lansoprazole** lie in between, as they are activated, at pH 5.0, about as quickly as they are eliminated from serum. The above activation rates refer to room temperature. At 37degreeC, the activation rates of all PPIs further increase, by about the same factor of between 3 and 4. This renders their differential pH selectivities even more critical for drug safety. Biological consequences have been reported in the literature. It has been claimed that a dose of 40 mg of the S-**enantiomer** of omeprazole (esomeprazole) results in 10%-15% higher healing rates in GERD patients, compared to 20 mg omeprazole racemate. The same difference is found when the two doses of omeprazole racemate are compared to each other. This is not surprising, as the chiral PPI prodrug is converted by acid into an achiral cyclic sulfenamide which only then reacts with the proton pump. There is therefore no pharmacodynamic argument in favour of any single **enantiomer** formulation of any PPI. Moreover, potential pharmacokinetic differences between the **enantiomers** seem to be of little if any importance in the patient.
CC Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508

Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Digestive System - Physiology and Biochemistry *14004
Digestive System - Pathology *14006
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
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Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014
Toxicology - Pharmacological Toxicology *22504

BC Hominidae 86215

IT Major Concepts
Gastroenterology (Human Medicine, Medical Sciences); Metabolism; Pharmacology

IT Parts, Structures, & Systems of Organisms
parietal cell: digestive system; serum: blood and lymphatics

IT Diseases
GERD [gastroesophageal reflux disease]: digestive system disease

IT Chemicals & Biochemicals
gastric proton-pump inhibitors: adverse effects, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics, pharmacokinetics, prodrug; **lansoprazole**: adverse effects, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics, pharmacokinetics; omeprazole: adverse effects, enzyme inhibitor - drug, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics, pharmacokinetics; pantoprazole: adverse effects, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics, pharmacokinetics; rabeprazole: adverse effects, gastric secretion inhibitor - drug, gastrointestinal - drug, pharmacodynamics, pharmacokinetics

IT Miscellaneous Descriptors
chirality; pH selectivity; serum elimination half-life

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): patient

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 103577-45-3 (**LANSOPRAZOLE**)
73590-58-6 (OMEPRAZOLE)
102625-70-7 (PANTOPRAZOLE)
117976-89-3 (RABEPRAZOLE)

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COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	178.64	178.85

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 15:11:50 ON 06 JAN 2003